Proposed Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N)

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Decision Summary

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

In the absence of a NCD, initial coverage determinations under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements will be made by the local Medicare Administrative Contractors (MACs) on an individual claim basis.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform the answer to the question posed in this proposed decision memorandum. Based on the gaps identified in the clinical evidence, these studies should focus on which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be developed that would support coverage with evidence development (CED), which would only cover gender reassignment surgery for beneficiaries who choose to participate in a clinical study.

ProposedDecision Memo

To: Administrative File: CAG #00446N

From: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Deputy Director, Coverage and Analysis Group

James Rollins, MD, PhD
Director, Division of Items and Devices

Elizabeth Koller, MD
Lead Medical Officer

Linda Gousis, JD
Lead Analyst

Katherine Szarama, PhD
Analyst

Subject: Proposed Decision Memorandum on Gender Reassignment Surgery for Medicare Beneficiaries with Gender Dysphoria

Date: June 2, 2016

I. Proposed Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

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II. Background

Below is a list of acronyms used throughout this document.

AHRQ - Agency for Healthcare Research and Quality
AIDS - Acquired Immune Deficiency Syndrome
ANOVA - Analysis of Variance
APA - American Psychiatric Association
APGAR - Adaptability, Partnership Growth, Affection, and Resolve test
BIQ - Body Image Questionnaire
BSRI - Bem Sex Role Inventory
CCEI - Crown Crips Experimental Index
CHIS - California Health Interview Survey
CI - Confidence Interval

CMS - Centers for Medicare & Medicaid Services
DAB - Departmental Appeals Board
DSM - Diagnostic and Statistical Manual of Mental Disorders
EMBASE - Exerpta Medica dataBASE
FBeK - Fragebogen zur Beurteilung des eigenen Korpers
FDA - Food and Drug Administration
FPI-R - Freiburg Personality Inventory
FSFI - Female Sexual Function Index
GAF - Global Assessment of Functioning
GID - Gender Identity Disorder
GIS - Gender Identity Trait Scale
GRS - Gender Reassignment Surgery
GSI - Global Severity Indices
HADS - Hospital Anxiety Depression Scale
HHS - U.S. Department of Health and Human Services
HIV - Human Immunodeficiency Virus
IIP - Inventory of Interpersonal Problems
IOM - Institute of Medicine
KHQ - King's Health Questionnaire
LGB - Lesbian, Gay, and Bisexual
LGBT - Lesbian, Gay, Bisexual, and Transgender
MAC - Medicare Administrative Contractor
MMPI - Minnesota Multiphasic Personality Inventory
NCA - National Coverage Analysis
NCD - National Coverage Determination
NICE - National Institute for Health Care Excellence
NIH - National Institutes of Health
NZHTA - New Zealand Health Technology Assessment
PIT - Psychological Integration of Trans-sexuals
QOL - Quality of Life
S.D. - Standard Deviation
SADS - Social Anxiety Depression Scale
SCL-90R - Symptom Check List 90-Revised
SDPE - Scale for Depersonalization Experiences
SES - Self Esteem Scale
SF - Short Form
SMR - Standardized Mortality Ratio
SOC – Standards of Care
STAI-X1 - Spielberger State and Trait Anxiety Questionnaire
STAI-X2 - Spielberger State and Trait Anxiety Questionnaire
TSCS - Tennessee Self-Concept Scale
U.S. - United States
VAS - Visual Analog Scale
WHOQOL-BREF - World Health Organization Quality of Life - Abbreviated version of the WHOQOL-100
WPATH - World Professional Association for Transgender Health

A. Diagnostic Criteria

The criteria for gender dysphoria or spectrum of related conditions as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has changed over time (See Appendix A).

Gender dysphoria (previously known as gender identity disorder) is a classification used to describe persons who experience significant discontent with their biological sex and/or gender assigned at birth. Therapeutic options for gender dysphoria include behavioral and psychotherapies, hormonal treatments, and a number of surgeries used for gender reassignment. This proposed decision is only focusing on gender reassignment surgery.

B. Prevalence of Gender Dysphoria

Prevalence of gender dysphoria estimates have been reported by several investigators.

For estimates of transgender individuals in the U.S., we looked at several studies.

The Massachusetts Behavior Risk Factor Surveillance Survey (via telephone) (2007 and 2009) identified 0.5% individuals as transgender (Conron et al., 2012).

Derivative data obtained from the 2004 California Lesbian Gay Bisexual and Transgender (LGBT) Tobacco Survey (via telephone) and the 2009 California Health Interview Survey (CHIS) (via telephone) suggested the LGB population constitutes 3.2% of the California population and that transgender subjects constitute approximately 2% of the California LGBT population and 0.06% of the overall California population (Bye et al., 2005; CHIS 2009; Gates, 2011).

In a recent review of Medicare claims data, CMS estimated that in calendar year 2013 there were at least 4,098 transgender beneficiaries (less than 1% of the Medicare population) who utilized services paid for by Medicare, of which 90% had confirmatory diagnosis, billing codes, or evidence of a hormone therapy prescription. The Medicare transgender population is racially and ethnically diverse (e.g., 74% White, 15% African American) and spans the entire country. The following states have at least 100 transgender beneficiaries: California, Florida, Georgia, Illinois, Massachusetts, Michigan, Minnesota, New York, Pennsylvania, Ohio, Texas, Washington, and Wisconsin. Nearly 80% of transgender beneficiaries are under age 65, including approximately 23% ages 45-54. Of note, for the transgender population under age 65, the most prevalent chronic conditions were depression, major depressive affective disorder, and anxiety. Approximately 75% of transgender Medicare beneficiaries have been affected by depression, which is a disproportionately high amount compared to the Medicare population as a whole with 14% of Medicare fee-for-service beneficiaries suffering from the disease (CMS, *Chronic Conditions Among Medicare Beneficiaries*, 2012 at https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/chronic-conditions/downloads/2012chartbook.pdf). Based on the claims data, about 48% of transgender beneficiaries use hormone therapy, which are coverable under the Medicare Part D prescription drug benefit program (CMS Office of Minority Health (2015, June). New Directions in CMS Disparities Research: Sexual Orientation & Gender Identity. Paper presented at the Academy Health Annual Research Meeting, Minneapolis, Minnesota and Gay and Lesbian Medical Association Meeting, Portland, Oregon).

For international comparison purposes, recent estimates of transgender populations in other countries are similar to those in the United States. New Zealand researchers, using passport data, reported a prevalence of 0.0275% for male-to-female adults and 0.0044% female-to-male adults (6:1 ratio) (Veale, 2008). Researchers from a centers of transgender treatment and reassignment surgery in Belgium conducted a survey of regional plastic surgeons and reported a prevalence of 0.008% male-to-female and 0.003% female-to-male (ratio 2.7:1) surgically reassigned transsexuals in Belgium (De Cuypere et al., 2007). Swedish researchers, using national mandatory reporting data on those requesting reassignment surgery, reported secular changes over time in that the number of completed reassignment surgeries per application increased markedly in the 1990s; the male-to-female/female-to-male sex ratio changed from 1:1 to 2:1; the age of male-to-female and female-to-male applicants was initially similar, but increased by eight years for male-to-female applicants; and the proportion of foreign born applicants increased (Olsson, Moller 2003).

C. Interventions

Table 1 provides information about some of the types of therapeutic interventions for transgender individuals.

Table 1. Types of Therapeutic Intervention (May Not be Exhaustive)

Treatment Category	Male to Female	Female to Male
HORMONAL[1]		
Core		
	Estrogens Anti-androgens (e.g., spirono-lactone, 5-ά reductase blockers, androgen receptor blockers, GnRH analogues)	Androgens Progestins/GnRH analogues for menses suppression as needed after 1 yr of androgens
SURGICAL[2,3]		
Natal Internal Genital Removal	Orchidectomy (testes)	Hysterectomy (uterus) and Salpingo-oopherectomy (fallopian tubes + ovaries)
Natal External Genital Removal	Penectomy	NA
Breast Removal	NA	Mastectomy
Genital Reconstruction[2]	Vaginoplasty Clitoroplasty Labioplasty Urethrostomy	Metoidioplasty or Phalloplasty Inflatable/rigid penile prosthesis insertion Scrotal reconstruction

RH=gonadotropin releasing hormone NA=not applicable ?=possible ↑=increased 2o=secondary

1—Bowman et al., 2012; Deutch, 2015; Elaut et al., 2010 Gooren et al., 2005 ,2013, and 2014; Heresova, 1986; Jacobeit, et al., 2009; Kronawitter et al., 2009; Meuller, 2010; Meyer et al., 1981; Pelusi et al., 2014; Schlatterer et al., 1998; Seal et al., 2012; Traish et al., 2010; Wierckx et al., 2011b, 2014; Williamson et al., 2010.

2—Revisions may be required. Kuhn et al., 2011.

3—Goddard et al., 2007a; Jain, Bradbeer, 2007; Selvaggi, Bellringer, 2011; Wroblewski et al., 2013.

III. History of Medicare Coverage

CMS does not currently have an NCD on gender reassignment surgery.

A. Current Request

On December 3, 2015, CMS accepted a formal complete request from a beneficiary to initiate a national coverage analysis (NCA) for gender reassignment surgery.

CMS opened this National Coverage Analysis (NCA) to thoroughly review the evidence to determine whether or not gender reassignment surgery may be covered nationally under the Medicare program.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For gender reassignment surgery, the

following are statutes are applicable to coverage:

Under §1812 (Scope of Part A)

Under §1832 (Scope of Part B)

Under §1861(s) (Definition of Medical and Other Health Services)

Under §1861(s)(1) (Physicians' Services)

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Table 2: Timeline of Medicare Coverage Policy Actions for Gender Reassignment Surgery

Date	Action
August 1, 1989	The Health Care Financing Agency (HCFA; predecessor agency to CMS) published the initial NCD, titled "140.3, Transsexual Surgery" in the Federal Register. (54 Fed. Reg. 34,555, 34,572)
May 30, 2014	The HHS Departmental Appeals Board (DAB) determined that the NCD denying coverage for all transsexual surgery was not valid. As a result, MACs determined coverage on a case-by-case basis.
December 3, 2015	CMS accepts an external request to open an NCD. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
January 2, 2016	Initial comment period closed. CMS received 103 comments.

V. FDA Status

Surgical procedures *per se* are not subject to the Food and Drug Administration's (FDA) approval.

Inflatable penile prosthetic devices, rigid penile implants, testicular prosthetic implants, and breast implants have been approved/cleared by the FDA.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical question relevant to the coverage request can be answered conclusively; and 2) the extent to

which we are confident that the intervention will improve health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer-reviewed medical journals. We considered articles cited by the requestor, in public comments, as well as those found by a CMS literature review. Citations are detailed below.

B. Literature Search Methods

CMS staff extensively searched for primary studies evaluating therapeutic interventions for gender dysphoria. There was particular emphasis on the various surgical interventions, but other treatments including hormone therapy, psychotherapy, psychiatric treatment, ancillary reproductive and gender modifying services, and post-operative surveillance services for natal sex organs were also included because of their serial and sometimes overlapping roles in patient management. The emphasis focused less on specific surgical techniques and more on functional outcomes unless specific techniques altered those types of outcomes.

The reviewed evidence included articles obtained by searching literature databases and technology review databases from PubMed (1965 to current date), EMBASE, the Agency for Healthcare Research and Quality (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies. Systematic reviews were used to help locate some of the more obscure publications and abstracts.

Keywords used in the search included: Trans-sexual, transgender, gender identity disorder (syndrome), gender dysphoria and/or hormone therapy, gender surgery, genital surgery, gender reassignment (surgery), sex reassignment (surgery) AND/OR quality of life, satisfaction-regret, psychological function (diagnosis of mood disorders, psychopathology, personality disorders), employment status, relationships, other social function, suicide (attempts), mortality, sexual function, urinary function, and adverse events-reoperations. After the identification of germane publications, CMS also conducted searches on the specific psychometric instruments used by investigators.

Psychometric instruments are scientific tools used to measure individuals' mental capabilities and behavioral style. They are usually in the form of questionnaires that numerically capture responses. These tools are used to create a psychological profile that can address questions about a person’s knowledge, abilities, attitudes and personality

traits. In the evaluation of patients with gender dysphoria, it is important that both validity and reliability be assured in the construction of the tool (validity refers to how well the tool actually measures what it was designed to measure, or how well it reflects the reality it claims to represent, while reliability refers to how accurately results of the tool would be replicated in a second identical piece of research). That is because when evaluating patients with this condition most of the variables of interest (e.g., satisfaction, anxiety, depression) are latent in nature (not directly observed but are rather inferred) and difficult to quantify objectively.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than small, pilot studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important. Studies with fewer than 30 patients were reviewed and delineated, but excluded from the major analytic framework. Oral presentations, unpublished white papers, and case reports were excluded. Publications in languages other than English were excluded.

Included studies were limited to those with adult subjects. Review and discussion of the management of children and adolescents with the additional considerations of induced pubertal delay are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. The excluded duplicative publications are delineated.

CMS also searched Clinicaltrials.gov to identify relevant clinical trials. CMS looked at trial status including early termination, completed, and ongoing with sponsor update, and ongoing with estimated date of completion. Publications on completed trials were sought. The CMS internal search was limited to articles published prior to March 21, 2016. CMS reviewed results of clinical trials involving adult human subjects; to reports of prospective (e.g., blinded, non-blinded, cross sectional), partially prospective, retrospective longitudinal studies randomized meeting certain criteria.

C. Discussion of Evidence

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" CMS is interested in answering the following question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

The evidence reviewed is directed towards answering this question.

1. Internal Technology Assessment

When looking at the studies evaluating gender reassignment surgery for patients with gender dysphoria, we found an array of disparate research designs. Most of the studies were conducted in Europe. Only six studies took place in the U.S. (Ainsworth, Spiegel, 2010; Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006; Lawrence, 2006; Leinung et al., 2013). Most of the studies that evaluated gender dysphoria were descriptive in nature; few made inferences which may be applicable to the Medicare population.

CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of

gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions. CMS also explored the relative roles that psychological support, mental health care, cross-sex hormonal therapy, and the various gender reassignment related surgical procedures played in health outcomes.

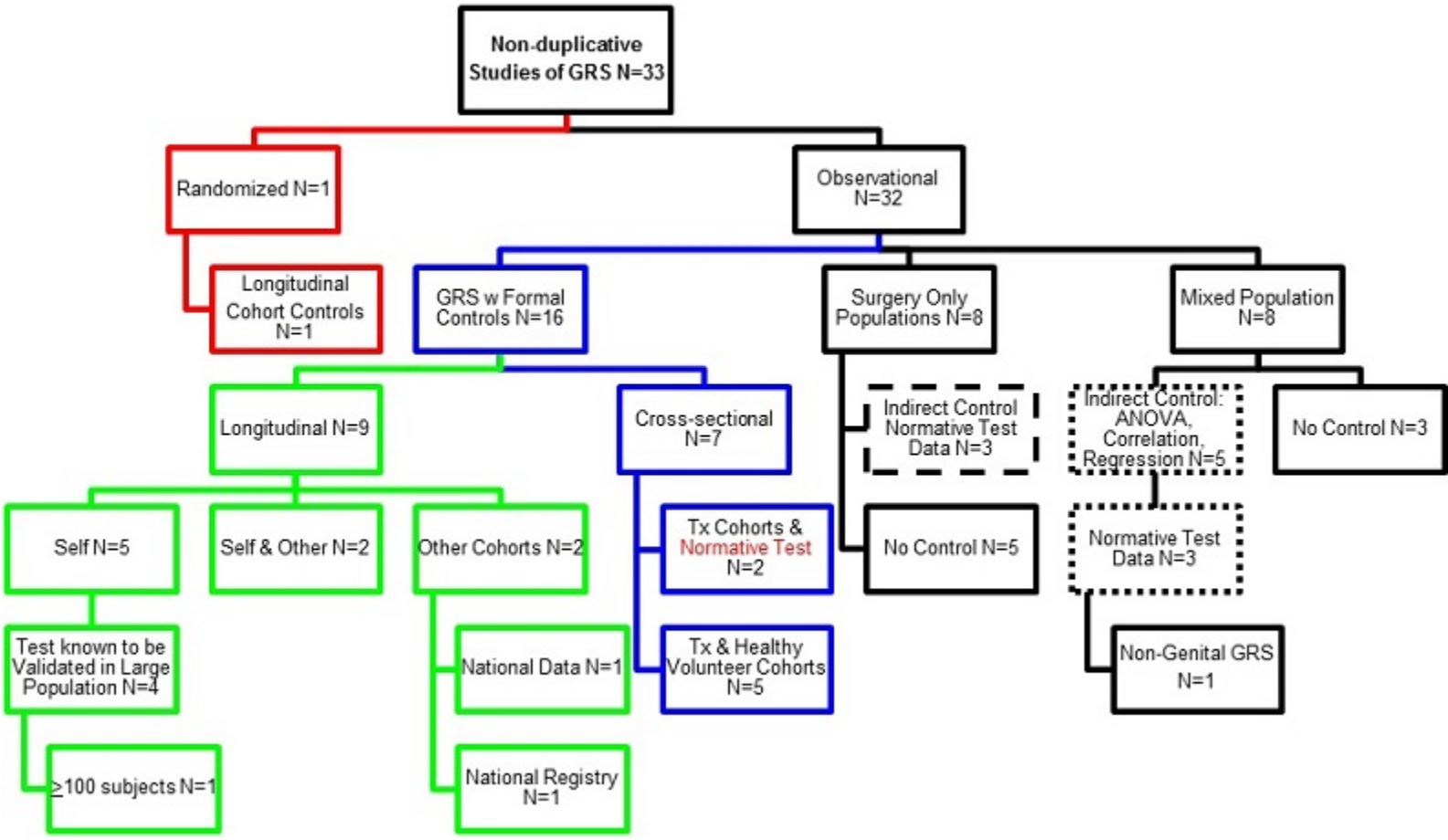
CMS identified numerous publications related to gender reassignment surgery. A large number of these were case reports, case series with or without descriptive statistics, or studies with population sizes too small to conduct standard parametric statistical analyses. Others addressed issues of surgical technique.

CMS identified and described 36 publications on gender reassignment surgery that included health outcomes. Because the various investigators at a site sometimes conducted serial studies on ever-enlarging cohort populations, studied sub-populations, studied different outcomes, or used different tools to study the same outcomes, not all study populations were unique. To reduce bias from over-lapping populations, only the latest or most germane publication(s) were described. Subsumed publications were delineated.

Of these 36 publications, two publications used different assessment tools on the same population, and, so for the purposes of evaluation, were classified as 1 study (Udeze et al., 2008; Megeri, Khoosal, 2007). For another publication, the complete manuscript could not be located despite an exhaustive search by the Library of Medicine (Barrett, 1998). This precluded adequate review, thus, it was not included. A total of 33 studies were reviewed (See Figure 1). Appendices C, D, and F include more detail of each study.

The publications covered a time span from 1979 to 2015. Over half of the studies were published after 2005.

Figure 1. Studies of Gender Reassignment Surgery (GRS)



ANOVA=Analysis of Variance Normative=Psychometric Tests with known normative for large populations

The studies in Figure 1 are categorized into 3 groups. The first group, depicted by the colored boxes (red, blue, and green), had explicit controls. There was a single randomized study. The remainder in the first group were observational studies. These were subdivided into longitudinal studies and cross-sectional studies. The second group, depicted by black boxes (starting with the surgery only populations box) consisted of surgical series. The third group, depicted by black boxes (starting with mixed population), was composed of mixed populations of patients not stratified by treatment and which included a spectrum of therapeutic interventions.

When looking at the totality of studies, they fell into the following research design groups:

a. <u>Prospective, non-blinded, observational, cross-sectional studies with no concurrent controls</u>

Ainsworth TA, Spiegel JH. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. Qual Life Res. 2010 Sep;19(7):1019-24.

Ainsworth and Spiegel conducted a prospective, observational study using a cross-sectional design and a partially self-designed survey tool. The blind status is unknown. Treatment types served as the basis for controls.

The investigators, head and neck surgeons who provided facial feminization services, assessed perception of appearance and quality of life in male-to-female subjects with self-reported gender dysphoria. Patients could have received no therapeutic intervention, hormone therapy, reassignment surgery, and/or facial feminization surgery and an unrestricted length of transition. (Transition refers to the time when a transgender person begins to live as the gender with which they identify rather than the gender assigned at birth.) Criteria for the various types of interventions were not available because of the survey design of the study. Patients were recruited via website or at a 2007 health conference. Pre-specified controls to eliminate duplicate responders were not provided. The investigators employed a self-designed Likert-style facial feminization outcomes evaluation questionnaire and a "San Francisco 36" health questionnaire. No citations were provided for the latter. It appears to be the Short-form (SF) 36-version 2. Changes or differences considered to be biologically significant were not pre-specified. Power corrections for multiple comparisons were not provided.

The investigators reported that there were 247 participants. (The numbers of incomplete questionnaires was not reported.) Of the 247 participants, 25 (10.1%) received only primary sex trait reassignment surgery, 28 (11.3%) received facial surgery without primary sex trait reassignment surgery, 47 (19.0%) received both facial and primary sex trait reassignment surgery, and 147 (59.5%) received neither facial nor reassignment surgery. The mean age for each of these cohorts was: 50 (no standard deviation [S.D.]) only reassignment surgery, 51 (no S.D.) only facial surgery, 49 (no S.D.) both types of surgery, and 46 (no S.D.) (neither surgery). Of the surgical cohorts: 100% of those who had undergone primary sex trait reassignment surgery alone used hormone therapy, 86% of those who had undergone facial feminization used hormone therapy, and 98% of those who had undergone both primary sex trait reassignment surgery and facial feminization used hormone therapy. In contrast to the surgical cohorts, 66% of the "no surgery" cohort used hormonal therapy, and a large proportion (27%) had been in transition for less than 1 year.

The investigators reported higher scores on the facial outcomes evaluation in those who had undergone facial feminization. Scores of the surgical cohorts for the presumptive SF-36 comprehensive mental health domain did not differ from the general U.S. female population. Scores of the "no surgery" cohort for the comprehensive mental health domain were statistically lower than those of the general U.S. female population, but within 1 standard deviation of the normative mean. Mean scores of all the gender dysphoric cohorts for the comprehensive physical domain were statistically higher than those of the general female U.S. population, but were well within 1 standard deviation of the normative mean. Analyses of inter-cohort differences for the SF-36 results were not conducted. Although the investigators commented on the potential disproportionate impact of hormone therapy on outcomes

and differences in the time in "transition", they did not conduct any statistical analyses to correct for putative confounding variables.

Motmans J , Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. J Sex Med. 2012 Mar;9(3):743-50. Epub 2011 Dec 21.

Motmans et al., conducted a prospective, non-blinded, observational study using a cross-sectional design and a non-specific quality-of-life tool. No concurrent controls were used in this study. Quality of life in this Dutch-speaking population was assessed using the Dutch version of a SF-36 (normative data was used). Participants included subjects who were living in accordance with the preferred gender and who were from a single, unspecified, Belgian university specialty clinic. The Dutch version of the SF-36 questionnaire along with its normative data were used. Variables explored included employment, pension status, ability to work, being involved in a relationship. Also explored, was surgical reassignment surgery and the types of surgical interventions. Intragroup comparisons by transgender category were conducted, and the relationships between variables were assessed by analysis of variance (ANOVA) and correlations.

The age of the entire cohort (n=140) was 39.89±10.21 (female-to-male: 37.03±8.51; male-to-female: 42.26±10.39). Results of the analysis revealed that not all female-to-male patients underwent surgical reassignment surgery and, of those who did, not all underwent complete surgical reassignment. The numbers of female-to-male surgical interventions were: mastectomy 55, hysterectomy 55, metadoiplasty 8 (with 5 of these later having phalloplasty), phalloplasty 40, and implantation of a prosthetic erectile device 20. The frequencies of various male-to-female surgical interventions were: vaginoplasty 48, breast augmentation 39, thyroid cartilage reduction 17, facial feminization 14, and hair transplantation 3.

The final number of subjects with SF-36 scores was 103 (49 [47.6%] female-to-male; 54 [52.4%] male-to-female; ratio 1:1.1). For this measure, the scores for the vitality and mental health domains for the final female-to-male cohort (n= 49 and not limited to those having undergone some element of reassignment surgery) were statistically lower: 60.61±18.16 versus 71.9±18.31 and 71.51±16.40 versus 79.3±16.4 respectively. Scores were not different from the normative data for Dutch women: vitality: 64.3±19.7 or mental health 73.7±18.2. None of the domains of the SF-36 for the final male-to-female cohort (n=54 and not limited to those having undergone some element of reassignment surgery) were statistically different from the normative data for Dutch women.

Analysis of variance indicated that quality-of-life as measured by the SF-36 did not differ by whether female-to-male patients had undergone genital surgery (metadoidoplasty or phalloplasty) or not. Also, ANOVA indicated that quality-of-life as measured by the SF-36 did not differ by whether male-to-female patients had undergone either breast augmentation or genital surgery (vaginoplasty) or not.

Whether there is overlap with the Ghent populations studied by Heylens et al., Weyers et al., or Wierckx et al. is unknown.

Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. J Sex Med. 2009 Mar;6(3):752-60. Epub 2008 Nov 17.

Weyers at al. 2009 conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments including a non-specific quality of life tool and a semi-specific quality of life tool (using normative data) along with 2 self-designed tools.

The investigators assessed general quality of life, sexual function, and body image from the prior 4 weeks in Dutch-speaking male-to-female patients with gender dysphoria who attended a single-center, specialized, comprehensive care university clinic. Investigators used the Dutch version of the SF-36 and results were compared to normative data from Dutch women and U.S. women. The 19 items of the Dutch version of the Female Sexual Function Index (FSFI) were used to measure sexual desire, function, and satisfaction. A self-designed 7 question visual analog scale (VAS) was used to measure satisfaction with gender related body traits and appearance perception by self and others. A self-designed survey measured a broad variety of questions regarding personal medical history, familial medical history, relationships, importance of sex, sexual orientation, gynecologic care, level of regret, and other health concerns. For this study, hormone levels were also obtained.

The study consisted of 50 participants. Analysis of the data revealed that the patient's average age was 43.1 ±10.4 years, and all of the patients had vaginoplasty. This same population also had undergone additional feminization surgical procedures (breast augmentation 96.0%, facial feminization 36.0%, vocal cord surgery 40.0%, and cricoid cartilage reduction 30.0%). A total of two (4.0%) participants reported "sometimes" regretting reassignment surgery and 23 (46.0%) were not in a relationship. For the cohort, estradiol, testosterone, and sex hormone binding globulin levels were in the expected range for the reassigned gender. The SF-36 survey revealed that the subscale scores of the participants did not differ substantively from those of Dutch and U.S. women. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

The total FSFI score was 16.95±10.04 out of a maximal 36. The FSFI scores averaged 2.8 (6 point maximum): satisfaction 3.46±1.57, desire 3.12+1.47, arousal 2.95±2.17, lubrication 2.39±2.29, orgasm 2.82±2.29, and pain 2.21±2.46. Though these numbers were reported in the study, data on test population controls were not provided. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

A *post hoc* exploration of the data was performed that revealed the following: perceived improvement in general health status was greater in the subset that had undergone reassignment surgery within the last year; sexual orientation impacted the likelihood of being in a relationship; SF-36 scores for vitality, social functioning, and mental health were nominally better for those in relationships, but that overall SF-36 scores did not differ by relationship status; sexual orientation and being in a relationship impacted FSFI scores; and reported sexual function was higher in those with higher satisfaction with regards to their appearance.

Wierckx K, Van Caenegem E, Elaut E, Dedecker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. J Sex Med. 2011 Dec;8(12):3379-88. Epub 2011 Jun 23.

Wierckx at al. conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments (a non-specific quality of life tool with reported normative data along with 3 self-designed tools). The investigators assessed general quality of life, sexual relationships, and surgical complications in Dutch-speaking female-to-male patients with gender dysphoria who attended a single-center, specialized, comprehensive care, university clinic. Investigators used the Dutch version of the SF-36 with 36 questions, 8 subscales, and 2 domains evaluating physical and mental health. Results were compared to normative data from Dutch women and Dutch men. Self -designed questionnaires to evaluate aspects of medical history, sexual functioning (there were separate versions for those with and without partners), and surgical results were also used. The Likert-style format was used for many of the questions.

A total of 79 female-to-male patients with gender dysphoria had undergone reassignment surgery were contacted;

however, ultimately, 47 (59.5%) chose to participate. Three additional patients were recruited by other patients. One of the 50 participants was later excluded for undergoing reassignment surgery within the 1 year window. The age of patients was: 30±8.2 years (range 16 to 49) at the time of reassignment surgery and 37.1 ±8.2 years (range 22 to 54) at the time of follow-up. The time since hysterectomy, oopherectomy, and mastectomy was 8 years (range 2 to 22). The patient population had undergone additional surgical procedures: metaidoiplasty (n=9; 18.4%), phalloplasty (n=8 after metaidoiplasty, 38 directly; 93.9% total), and implantation of erectile prosthetic device (n=32; 65.3%). All had started hormonal therapy at least 2 years prior to surgery and continued to use androgens.

The SF-36 survey was completed by 47 (95.9%) participants. The "Vitality" and the "Mental Health" scales were lower than the Dutch male population: 62.1±20.7 versus 71.9±18.3 and 72.6±19.2 versus 79.3±16.4 respectively. These subscale scores were equivalent to the mean scores of the Dutch women.

None of the participants were dissatisfied with their hysterectomy-oopherectomy procedures; 4.1% were dissatisfied with their mastectomies because of extensive scarring; and 2.2% were dissatisfied with their phalloplasties. Of the participants, 17.9% were dissatisfied with the implantation of an erectile prosthetic device; 25 (51.0%) reported at least one post-operative complication associated with phalloplasty (e.g., infection, urethrostenosis, or fistula formation); 16 (50.0% of the 32 with an erectile prosthetic device) reported at least one post-operative complication associated with implantation of an erectile prosthetic (e.g., infection, leakage, incorrect positioning, or lack of function).

A total of 18 (36.7%) participants were not in a relationship; 12.2% reported the inability to achieve orgasm with self-stimulation less than half the time; 12.2% did not respond to the question. Of those with participants with partners, 28.5% reported the inability to achieve orgasm with intercourse less than half the time and 9.7% did not respond to this question. Also, 61.3% of those with partners reported (a) no sexual activities (19.4%) or (b) activities once or twice monthly (41.9%), and there were 12.9% who declined to answer.

Post hoc assessments suggested that being in relationship or having undergone phalloplasty did not impact the scores of the SF-36 domains. Also this assessment suggested that for patients in a relationship, sexual satisfaction was related to "Vitality" scores. Finally this assessment suggested a relationship between sexual satisfaction and more frequent orgasm and pleasure with the partner.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. Psychiatry Clin Neurosci. 2012 Jun;66(4):371-2. PMID: 22624747.

Salvador et al. conducted a prospective, non-blinded, observational study using a cross-sectional design (albeit over an extended time interval) and a self-designed quality of life tool. The investigators assessed regret, sexual function, partnerships, and family relationships in patients who had undergone gender reassignment surgery at least 24 months prior.

Out of the 243 enrolled in the clinic over a 10 year interval, 52 patients agreed to participate in the study. The age at follow-up was 36.3±8.9 (range 15-58) years with the time to follow-up being 3.8±1.7 (2-7) years. A total of 46 participants reported pleasurable neo-vaginal sex and post-surgical improvement in the quality of their sexual experience. The quality of sexual intercourse was rated as satisfactory to excellent, average, unsatisfactory, or not applicable in the absence of sexual contact by 84.6%, 9.6%, 1.9%, and 3.8% respectively. Of the participants, 78.8% reported greater ease in initiating and maintaining relationships; 65.4% reported having a partner; 67.3% reported increased frequency of intercourse; 36.8% reported improved familial relationships. No patient reported regret over reassignment surgery. The authors did not provide information about incomplete questionnaires.

Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. J Consult Clin Psychol. 1985 Jun;53(3):295-304.

Blanchard et al. conducted a prospective, non-blinded, cross-sectional study using a self-designed questionnaire and a non-specific psychological symptom assessment with normative data. The investigators assessed social adjustment and psychopathology in patients with gender dysphoria and who were at least 1 year post gender reassignment surgery. Reassignment surgery was defined as either vaginoplasty or mastectomy/construction of male chest contour with or without nipple transplants, but did not preclude additional procedures. Partner preference was determined using the Modified Androphilia-Gynephilia Index, and the nature and extent of any psychopathology was determined with the Symptom Check List 90-Revised (SCL-90R).

Of the 294 patients (111 natal females and 183 natal males, ratio: 1:1.65) initially evaluated, 79 patients participated in the study (38 female-to-male; 32 male-to-female with male partner preference; 9 male-to-female with female partner preference). The respective mean ages for these 3 groups were 32.6, 33.2, and 47.7 years with the last group being older statistically (p=0.01). Additional surgeries in female-to-male patients included: oophorectomy/hysterectomy 92.1% and phalloplasty 7.9%. Additional procedures in male-to-female patients with male partner preference included facial hair electrolysis 62.5% and breast implantation 53.1%. Additional procedures in male-to-female patients with female partner preference included facial hair electrolysis 100% and breast implantation 33.3%. The time between reassignment surgery and questionnaire completion did not differ by group.

Psychopathology as measured by the Global Severity Index of the SCL-90R was absent in all 3 patient groups. Interpretation did not differ by the sex of the normative cohort.

Of participants, 63.2% of female-to-male patients cohabitated with partners of their natal gender. 46.9% of male-to-female patients with male partner preference cohabitated with partners of their natal gender; 93.7% reported that they would definitely undergo reassignment surgery again. The remaining 6.3% (1 female-to-male; 1 male-to-female with male partner preference; 3 male-to-female with female partner preference) indicated that they probably would undertake the surgery again. *Post hoc* analysis suggested that the more ambivalent responders had more recently undergone surgery. Of responders, 98.7% indicated that they preferred life in the reassigned gender. The one ambivalent subject was a skilled and well compensated tradesperson who was unable to return to work in her male dominated occupation.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. Singapore Med J. 1993 Dec;34(6):515-7.

Tsoi conducted a prospective, non-blinded, observational study using a cross-sectional design and a self-designed quality of life tool. The investigators assessed overall life satisfaction, employment, partner status, and sexual function in gender-reassigned persons who had undergone gender reassignment surgery between 1972 and 1988 inclusive and who were approximately 2 to 5 years post-surgery. Acceptance criteria for surgery included good physical health, good mental health, absence of heterosexual tendencies, willingness to undergo hormonal therapy for ≥6 months, and willingness to function in the life of the desired gender for ≥6 months. Tsoi also undertook retrospective identification of variables that could predict outcomes.

The size of the pool of available patients was not identified. Of the 81 participants, 36 were female-to-male (44.4%) and 45 were male-to-female (55.6%) (ratio 1:1.25).

The mean ages at the time of the initial visit and operation were: female-to-male 25.4±4.4 (range 14-36) and 27.4 ±4.0; (range 14-36); male-to-female 22.9±4.6 (range 14-36) and 24.7±4.3 (14-36) years respectively. Of all participants, 14.8% were under age 20 at the time of the initial visit. All were at least 20 at the time of gender reassignment surgery. The reported age of onset was 8.6 years for female-to-male patients and 8.7 years for male-

to-female patients.

All participants reported dressing without difficulty in the reassigned gender; 95% of patients reported good or satisfactory adjustment in employment and income status; 72% reported good or satisfactory adjustment in relationships with partners. Although the quality of life tool was self-designed, 81% reported good or satisfactory adjustment to their new gender, and 63% reported good or acceptable satisfaction with sexual activity. Of the female-to-male patients, 39% reported good or acceptable satisfaction with sex organ function in comparison to 91% of male-to-female patients ($p<0.001$). (The author reported that a fully functioning neo-phallus could not be constructed at the time.) The age of non-intercourse sexual activity was the only predictor of an improved outcome.

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012 May;37(5):662-70. Epub 2011 Sep 19.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a cross-sectional design and non-specific psychiatric distress tools in Spain. The investigators assessed anxiety and depression in patients with gender dysphoria who attended a single-center specialty clinic with comprehensive endocrine, psychological, psychiatric, and surgical care. The clinic employed World Professional Association for Transgender Health (WPATH) guidelines. Patients were required to have met diagnostic criteria during evaluations by 2 experts. Investigators used the Hospital Anxiety and Depression Scale (HADS) and the Social Anxiety and Distress Scale (SADS) instruments. The SADS total score ranges from 0 to 28, with higher scores indicative of more anxiety. English language normative values are 9.1±8.0. HAD-anxiety and HAD-depression total score ranges from 0 to 21, with higher scores indicative of more pathology. Scores less than 8 are normal. ANOVA was used to explore effects of hormone and surgical treatment.

Of the 200 consecutively selected patients recruited, 187 (93.5% of recruited) were included in the final study population. Of the final study population, 74 (39.6%) were female-to-male patients; 113 (60.4%) were male-to-female patients (ratio 1:1.5); and 120 (64.2%) were using hormones. Of those using hormones, 36 (30.0%) were female-to-male; 84 (70.0%) were male-to-female (ratio 1:2.3). The mean age was 29.87±9.15 (range 15-61). The current age of patients using hormones was 33.6±9.1 (n=120) and older than the age of patients without hormone treatment (25.9±7.5) ($p=0.001$). The age at hormone initiation, however, was 24.6±8.1.

Of those who had undergone reassignment surgery, 29 (36.7%) were female-to-male; 50 (63.3%) were male-to-female; ratio 1:1.7. The number of patients not on hormones and who had undergone at least 1 gender-related surgical procedure (genital or non-genital) was small (n=2). The number of female-to-male patients on hormones who had undergone such surgery (mastectomy, hysterectomy, or phalloplasty) was 28 (77.8%). The number of male-to-female patients on hormones who had undergone such surgery (mammoplasty, facial feminization, buttock feminization, vaginoplasty, orchiectomy, and vocal feminization (thyroid chondroplasty) was 49 (58.3%).

Analysis of the data revealed that although the mean scores HAD-Anxiety, HAD-Depression, and SADS were statistically lower (better) in those on hormone therapy than in those not on hormone therapy, the mean scores for HAD-Depression and SADS were in the normal range for gender dysphoric patients not using hormones. The HAD-Anxiety score was borderline elevated and consistent with a possible mood disorder in patients not using hormones. The mean scores for HAD-Anxiety, HAD-Depression, and SADS were in the normal range for gender dysphoric patients using hormones. ANOVA revealed that results did not differ by whether the patient had undergone a gender related surgical procedure or not.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-

76. Epub 2013 Aug 13.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a non-specific quality of life tool. There were no formal controls for this mixed population ± non-genital reassignment surgery. The investigators assessed quality of life in the context of culture in patients with gender dysphoria who were from a single-center, specialty and gender identity clinic. The clinic used WPATH guidelines. Patients were required to have met diagnostic criteria during evaluations by both a psychologist and psychiatrist. Patients could have undergone non-genital surgeries, but NOT genital reassignment surgeries (e.g., orchiectomy, vaginoplasty, or phalloplasty).

The Spanish version of the World Health Organization Quality of Life-Abbreviated version of the WHOQOL-100 (WHOQOL-BREF) was used to evaluate quality-of-life, which has 4 domains (environmental, physical, psychological, and social) and 2 general questions. Family dynamics were assessed with the Spanish version of the Family Adaptability, Partnership Growth, Affection, and Resolve (APGAR) test. Regression analysis was used to explore effects of surgical treatment.

Of the 277 patients recruited, 260 (93.9%) agreed to participate. Of this number, 193 were included in the study (the mean age of this group was 31.2±9.9 (range 16-67). Of these, 74 (38.3%) were female-to-male patients; 119 (61.7%) were male-to- female patients; ratio1:1.6. 120 (62.2%) were on hormone therapy; 29 (39.2%) of female-to-male patients had undergone at least 1 non-genital, surgical procedure (hysterectomy n=19 (25.7%); mastectomy n=29 (39.2%)); 51 (42.9%) of male-to-female patients had undergone at least 1 non-genital surgical procedure with mammoplasty augmentation being the most common procedure, n=47 (39.5%), followed by facial feminization, n=11 (9.2%), buttocks feminization, n=9 (7.6%), and vocal feminization (thyroid chondroplasty), n=2 (1.7%).

WHOQOL-BREF domain scores for gender dysphoric patients with and without non-genital surgery were: "Environmental" 58.81±14.89 (range 12.50-96.88), "Physical" 63.51±17.79 (range 14.29-100), "Psychological" 56.09+16.27 (range 16.67-56.09), "Social" 60.35±21.88 (range 8.33-100), and "Global QOL and Health" 55.44+27.18 (range 0-100). The mean APGAR family score was 7.23±2.86 (range 0-10).

Regression analysis, which was used to assess the relative importance of various factors to WHOQOL-BREF domains and general questions, revealed that family support was an important element for all 4 domains and the general health and quality-of-life questions. Hormone therapy was an important element for the general questions and for all of the domains except "Environmental." Having undergone non-genital reassignment surgery, like age, educational levels, and partnership status, did not impact domain and general question results related to quality of life.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. Br J Psychiatry. 1988 Apr;152:550-3.

Mate-Kole at al. conducted a prospective non-blinded, observational study using a cross-sectional design and 2 psychological tests (1 with some normative data). Concurrent controls were used in this study design. The investigators assessed neuroticism and sex role in natal males with gender dysphoria. Patients at various stages of management, (i.e., under evaluation, using cross-sex hormones, or post reassignment surgery [6 months to 2 years]) were matched by age of cross-dressing onset, childhood neuroticism, personal psychiatric history, and family psychiatric history. Both a psychologist and psychiatrist conducted assessments. The instruments used were the Crown Crisp Experiential Index (CCEI) for psychoneurotic symptoms and the Bem Sex Role Inventory. ANOVA was used to identify differences between the three treatment cohorts.

For each cohort, investigators recruited 50 male-to-female patients. The mean ages of the three cohorts were as follows: undergoing evaluation: mean age 34 years; wait-listed: mean age 35 years; and post-operative: mean age

37 years. Of the groups under evaluation or postsurgical, 16% (8 each) were unemployed; 8% of the waited listed patients were unemployed. For the cohorts, 22% of those under evaluation, 24% of those on hormone treatment only, and 30% of those post-surgery had prior psychiatric histories, and 24%, 24%, and 14% of the same respective cohorts had a history of attempted suicide. More than 30% of patients in each cohort had a first degree relative with a history of psychiatric disease.

The scores for the individual CCEI domains for depression and somatic anxiety were relatively higher (worse) for patients under evaluation than those on hormone treatment alone. The scores for all of the individual CCEI domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were lower in the post-operative cohort than in the other 2 cohorts.

The Bem Sex Role Inventory masculinity score for the combined cohorts was lower than for North American norms for either men or women. The femininity score for the combined cohorts was higher than for North American norms for either men or women. Those who were undergoing evaluation had the most divergent scores from North American norms and from the other treatment cohorts. Absolute differences were small. All scores of gender dysphoric patients averaged between 3.95 and 5.33 on a 7 point scale while the normative scores averaged between 4.59 and 5.12.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg. 1997 Mar;31(1):39-45.

Eldh et al. conducted a non-blinded, observational study using a prospective cross-sectional design with a self-designed questionnaire and retrospective acquisition of pre-operative data. The investigators assessed economic circumstances, family status, satisfaction with surgical results, and sexual function in patients who had undergone gender reassignment surgery. Of the 175 patients who underwent reassignment surgery in Sweden, 90 responded. Of this number, 50 were female-to-male and 40 were male-to-female (ratio: 1:0.8). Patients reportedly were generally satisfied with the appearance of the reconstructed genitalia (no numbers provided). Of the patients who had undergone surgery prior to 1986, seven (14%) were dissatisfied with shape or size of the neo-phallus; 8 (16%) declined comment. There were 14 (35%), with 12 having surgery prior to 1986 and two between 1986 and 1995 inclusive, were moderately satisfied because of insufficient vaginal volume; 8 (20%) declined comment. A neo-clitoris was not constructed until the later surgical cohort. Three of 33 reported no sensation or no sexual sensation. Eight had difficulties comprehending the question and did not respond.

A total of nine (18%) patients had doubts about their gender orientation; 13 (26%) declined to answer the question; 44 (27 [61.3%] female-to-male and 17 [38.6%] male-to-female) were unmarried or without a steady partner; 19 (38.0%) female-to-male patients reported the absence of a sex life (28.0% declined to answer this particular question); 15 (30%) male-to-female reported dissatisfaction with their sex lives. Additionally, 3 (6.0%) reported absence of sexual activity post-operatively. Ten (11.1%) were dissatisfied with their life situation (17.8% declined to answer this question). The study found that 2 female-to-male patients and 2 male-to-female patients regretted their reassignment surgery and continued to live as the natal gender, and two patients attempted suicide.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005 Mar;58(3):259-61.

Hepp et al. conducted a prospective, non-blinded, observational study using a cross-sectional design. There was some acquisition of retrospective data. The investigators assessed current and lifetime psychiatry co-morbidity using structured interviews for diagnosis of Axis 1 disorders (clinical syndromes) and Axis 2 disorders (developmental or personality disorders) and HADS for dimensional evaluation of anxiety and depression. Statistical description of the cohort and intra-group comparisons was performed. Continuous variables were compared using t-tests and ANOVA.

A total of 31 patients with gender dysphoria participated in the study: 11 (35.5%) female-to-male; 20 (64.5%) male-to-female (ratio 1:1.8). The overall mean age was 32.2±10.3. Of the participants, seven had undergone reassignment surgery, 10 pre-surgical patients had been prescribed hormone therapy, and 14 pre-surgical patients had not been prescribed hormone therapy. Forty five and one half percent of female-to-male and 20% of male-to-female patients did not carry a lifetime diagnosis of an Axis 1 condition. Sixty three and six tenths percent of female-to-male and 60% of male-to-female patients did not carry a current diagnosis of an Axis 1 condition. Lifetime diagnosis of substance abuse and mood disorder were more common in male-to-female patients (50% and 55% respectively) than female-to-male patients (36.4% and 27.3% respectively). Current diagnosis of substance abuse and mood disorder were present in male-to-female patients (15% and 20% respectively) and absent in female-to-male patients. One or more personality disorders were identified 41.9%, but whether this was a current or lifetime condition was not specified. Of the patients, five (16.1%) had a Cluster A personality disorder (paranoid-schizoid), seven (22.6%) had a Cluster B personality disorder (borderline, anti-social, histrionic, narcissistic), six (19.4%) had a Cluster C personality disorder (avoidant, dependent, obsessive-compulsive), and two (6.5%) were not otherwise classified.

The HADS test revealed non-pathologic results for depression (female-to-male: 6.64±5.03; male-to-female: 6.58±4.21) and borderline results for anxiety (female-to-male: 7.09±5.11; male-to-female: 7.74±6.13, where a result of 7-10 = possible disorder). There were no differences by natal gender. HADS scores were missing for at least 1 person. The investigators reported a trend for less anxiety and depression as measured by HADS in the patients who had undergone surgery.

b. <u>Prospective, non-blinded, observational, cross-sectional studies with patients serving as their own controls</u>

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. Arch Sex Behav. 1996 Oct;25(5):515-25.

Rakic et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and an investigator-designed quality of life tool that asked longitudinal (pre- and post-treatment) questions. Patients served as their own controls. The authors state that the study was not designed to assess the predictors of poor outcomes.

The investigators assessed global satisfaction, body image, relationships, employment status, and sexual function in patients with gender dysphoria who underwent reassignment surgery between 1989 and 1993 and were at least 6 months post-operative. The criteria to qualify for gender surgery were delineated (1985 standards from the Harry Benjamin International Gender Dysphoria Association) and included cross-gender behavior for at least 1 year. The questionnaire consisted of 10 questions using yes/no answers or Likert-type scales. Findings were descriptive without statistical analysis. As such, changes or differences considered to be biologically significant were not pre-specified, and there were no adjustments for multiple comparisons.

Of the 38 patients who had undergone reassignment surgery, 32 participated in the study 10 (31.2%) female-to-male and 22 (68.8%) male-to-female (ratio 1:2.2). The duration of follow-up was 21.8 ±13.4 months (range 6 months to 4 years). The age was female-to-male 27.8±5.2 (range 23-37) and male-to-female 26.4±7.8 (range 19-47).

Using an investigator-designed quality of life tool, all patients reported satisfaction with having undergone the surgery. Of the total participants, four (12.5%) (all male-to-female) and 8 (25%) (87.5% male-to-female) reported complete dissatisfaction or partial satisfaction with their appearance. Regarding relationships, 80% of female-to-male and 100% of male-to-female patients were dissatisfied with their relationships with others prior to surgery; whereas, no female-to-male patients and 18.1% of male-to-female patients were dissatisfied with relationships after surgery.

Regarding sexual partners, 60% of female-to-male and 72.7% of male-to-female patients reported not having a sexual partner prior to surgery; whereas, 20% of female-to-male patients and 27.3% of male-to-female patients did not have a sexual partner after surgery. Of those with partners at each time interval, 100% of female-to-male and 50% of male-to-female patients reported not experiencing orgasm prior to surgery; whereas, 75% of female-to-male and 37.5% of male-to-female patients reported not experiencing orgasm after surgery. Fifty percent of female-to-male and 54.5% of male-to-female patients reported being either unemployed or not being a student full-time prior to surgery. After surgery, no female-to-male patients and 7 (31.8%) male-to-female patients reported being either unemployed or not being a student full-time. The change was due to student status. Six (60%) of female-to-male patients and 15 (68.2%) of male-to-female patients reported being unemployed before and after surgery.

c. <u>Prospective, non-blinded, observational, cross-sectional studies with controls</u>

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. Arch Sex Behav. 2001 Jun;30(3):301-10.

Wolfradt and Neumann conducted a controlled, prospective, non-blinded, observational study using a cross-sectional design. The investigators assessed aspects of personality in male-to-female patients who had undergone vocal cord surgery for voice feminization and in healthy volunteers from the region. The patients had undergone gender reassignment surgery 1 to 5 years prior to voice surgery. The volunteers were matched by age and occupation. The primary hypothesis was that depersonalization, with the sense of being detached from one's body or mental processes, would be more common in male-to-female patients with gender dysphoria. German versions of the Scale for Depersonalization Experiences (SDPE), the Body Image Questionnaire (BIQ), a Gender Identity Trait Scale (GIS), and the Self-Esteem Scale (SES) were used in addition to a question regarding global satisfaction. Three of the assessments used a 5 point scale (BIQ, GIS, and SDPE) for questions. One used a 4 point scale (SES). Another used a 7 point scale (global satisfaction). The study consisted of 30 male-to-female patients, 30 healthy female volunteers, and 30 healthy male volunteers. The mean age of study participants was 43 (range 29-67).

Results of the study revealed that there were no differences between the three groups for the mean scores of measures assessing depersonalization, global satisfaction, the integration of masculine traits, and body-image-rejected (subset). Also, the sense of femininity was equivalent for male-to-female patients and female controls and higher than that in male controls. The levels of self-esteem and body image-dynamic (subset) were equivalent for male-to-female patients and male controls and higher than that in female controls, and none of the numeric differences between means exceeded 0.61 units.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. J Nerv Ment Dis. 1985 Jun;173(6):358-65. (United States study)

Beatrice conducted a prospective, non-blinded, observational study using a cross-sectional design and control cohorts in the U.S. The investigator assessed psychological adjustment and functioning (self-acceptance) in male-to-female patients with gender dysphoria (with and without gender reassignment surgery [GRS]), transvestites from two university specialty clinics, and self-identified heterosexual males recruited from the same two universities. The criteria to qualify for the study included being known to the clinic for at least one year, cross-dressing for at least one year without arrest, attendance at 10 or more therapy sessions, emotionally self-supporting, and financially capable of payment for reassignment surgery, and all of these criteria were met by the pre-operative cohort as well as the post-operative cohort. The cohorts were matched to the post-operative cohort (age, educational level, income, ethnicity, and prior heterosexual object choice). The post-operative cohort was selected not on the basis of population representation, but on the basis of demographic feasibility for a small study. The instruments used were the Minnesota Multiphasic Personality Inventory (MMPI) and the Tennessee Self-Concept Scale (TSCS). Changes or differences considered to be biologically significant were not pre-specified.

Of the initial 54 recruits, ten subjects were left in each of the cohorts because of exclusions identified due to demographic factors. The mean age of each cohort were as follows: pre-operative gender dysphoric patients 32.5 (range 27-42) years, postoperative patients 35.1 (30-43) years old, transvestite 32.5 (29-37) years old, and heterosexual male 32.9 (28-38) years old. All were Caucasian. The mean age for cross-dressing in pre-operative patients (6.4 years) and post-operative patients (5.8 years) was significantly lower than for transvestites (11.8 years).

The scores for self-acceptance did not differ by diagnostic category or surgical status as measured by the TSCS instrument. As measured by the T-scored MMPI instrument (50±10), levels of paranoia and schizophrenia were higher for post-operative (GRS) patients (63.0 and 68.8) than transvestites (55.6 and 59.6) and heterosexual males (56.2 and 51.6). Levels of schizophrenia were higher for pre-operative patients (65.1) than heterosexual males (51.6). There were no differences between patients with gender dysphoria by surgical status. Scores for the Masculine-Feminine domain were equivalent in those with transvestitism and gender dysphoria with or without surgery, but higher than in heterosexual males. The analysis revealed that despite the high level of socio-economic functioning in these highly selected subjects, the MMPI profiles based on the categories with the highest scores were notable for antisocial personality, emotionally unstable personality, and possible manic psychosis in the pre-operative GRS patients and for paranoid personality, paranoid schizophrenia, and schizoid personality in the post-operative GRS patients. By contrast, the same MMPI profiling in heterosexual males and transvestites was notable for the absence of psychological dysfunction.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology. 2008;41(2):96-100. Epub 2007 Nov 23.

Kraemer et al. conducted a prospective, non-blinded, observational study using a cross-sectional design comparing pre-and post-surgical cohorts. The investigators assessed body image, and patients were required to meet DSM III or DSM IV criteria as applicable to the time of entry into the clinic. Post-surgical patients were from a long-term study group (Hepp et al., 2002). Pre-surgical patients were recent consecutive referrals. The assessment tool was the Fragebogen zur Beurteilung des eigenen Korpers (FBeK) which contained 3 domains.

There were 23 pre-operative patients: 7 (30.4%) female-to-male and 16 (69.6%) male-to-female (ratio 1:2.3). There were 22 post-operative patients: 8 (36.4 %) female-to-male and 14 (63.6%) male-to-female (ratio 1:1.8). The mean ages of the cohorts were as follows: pre-operative 33.0±11.3 years; post-operative 38.2±9.0 years. The mean duration after reassignment surgery was 51±25 months (range 5-96).

The pre-operative groups had statistically higher insecurity scores compared to normative data for the natal sex: female-to-male 9.0±3.8 versus 5.1±3.7; male-to-female 8.1±4.5 versus 4.7±3.1 as well as statistically lower self-confidence in one's attractiveness: female-to-male 3.1±2.9 versus 8.9±3.1; male-to-female 7.0±2.9 vs 9.5±2.6. Scores for insecurity and self-confidence in the post-operative cohort were not inferior to the normative values. Insecurity decreased statistically from 9.0±3.8 in the female-to-male pre-operative cohort and from 8.1±4.5 in the male-to-female pre-operative cohort to 4.4±3.8 and 3.4±2.3 in the respective post-operative cohorts. Self-confidence increased statistically from 3.1±2.9 in the female-to-male pre-operative cohort and 7.0±2.9 male-to-female pre-operative cohort to 9.29±1.98 and 10.29±2.0 in the respective post-operative cohorts.

d. <u>Prospective, non-blinded, observational, cross-sectional studies with semi-matched controls</u>

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril. 2009 Nov;92(5):1685-1689.e3. Epub 2008 Nov 6.

Kuhn et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and semi-

matched control cohort. The investigators assessed global satisfaction in patients who were from gynecology and endocrinology clinics, and who had undergone some aspect of gender reassignment surgery in the distant past, but were still receiving cross-sex hormones from the clinic. The quality-of-life assessment tools included a VAS and the King's Health Questionnaire (KHQ) with its eight domains including one for incontinence. The KHQ questionnaire and the numerical change/difference required for clinical significance (≥5 points in a given domain, with higher scores being more pathologic) were included in the publication. Twenty healthy female controls from the medical staff who had previously undergone an abdominal or pelvic surgery were partially matched by age and body mass index (BMI), but not sex.

Of the 55 participants, three (5.4%) were female-to-male and 52 (94.5%) were male-to-female (ratio 1:17.3). Reassignment surgery had been conducted 8 to 23 years earlier (median 15 years). The median age of the patients at the time of the study was 51 years (range 39-62 years). The patients had undergone a median of 9 surgical procedures in comparison to the 2 undergone by controls. Patients were less likely to be married (23.6% versus 65%; p=0.002), and partnership status was unknown in 5 patients. The scores of VAS global satisfaction (maximal score 8) were lower for surgically reassigned patients (4.49±0.1 SEM) than controls (7.35±0.26 SEM) (p<0.0001).

There were statistically and biologically significant differences for 4 of the 8 domains between the patients and controls: physical limitation: 37.6±2.3 versus 20.9±1.9 (p0.0001), personal limitation: 20.9±1.9 versus 11.6±0.4 (p<0.001), role limitation: 27.8+2.4 versus 34.6+1.7 (p<0.5), and general health: 31.7±2.2 versus 41.0±2.3 (p<0.02). Information as to whether a high or low score was positive for the various domains was not provided. Wording from the abstract suggests that these 4 differences all reflected lower quality-of-life.

e. <u>Prospective, blinded, observational, cross-sectional studies with no concurrent controls</u>

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. Dtsch Arztebl Int. 2014 Nov 21;111(47):795-801.

Hess at al. conducted a prospective, blinded, observational study using a cross-sectional design and a self-designed questionnaire. The investigators assessed post-operative satisfaction in male-to-female patients with gender dysphoria who were followed in a urology specialty clinic. Patients had met the ICD-10 diagnostic criteria, undergone gender reassignment surgeries including penile inversion vaginoplasty, and a Likert-style questionnaire survey with 11 elements. Descriptive statistics were provided.

There were 254 consecutive eligible patients who had undergone surgery between 2004 and 2010 identified and sent surveys, of whom 119 (46.9%) responded anonymously. Of the participants, 13 (10.9%) reported dissatisfaction with outward appearance and 16 (13.4%) did not respond; three (2.5%) reported dissatisfaction with surgical aesthetics and 25 (21.0%) did not respond; eight (6.7%) reported dissatisfaction with functional outcomes of the surgery and 26 (21.8%) did not respond; 16 (13.4%) reported they could not achieve orgasm and 28 (23.5%) did not respond; four (3.4%) reported feeling completely male/more male than female and 28 (23.5%) did not respond; six (5.0%) reported not feeling accepted as a woman, two (1.7%) did not understand the question, and 17 (14.3%) did not respond; and 16 (13.4%) reported that life was harder and 24 (20.2%) did not respond.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. (United States study)

Lawrence conducted a prospective, blinded observational study using a cross-sectional design and a partially self-designed quality of life tool using yes/no questions or Likert scales. The investigator assessed sexual function, urinary function, and other pre/post-operative complications in patients who underwent male-to-female gender reassignment surgery. Questions addressed core reassignment surgery (neo-vagina and sensate neo-clitoris) and

related reassignment surgery (labiaplasty, urethral meatus revision, vaginal deepening/widening, and other procedures), use of electrolysis, and use of hormones.

Questionnaires were designed to be completed anonymously and mailed to 727 eligible patients. Of those eligible, 232 (32%) returned valid questionnaires. The age at the time reassignment surgery was 44±9 (range 18-70) years and mean duration after surgery was 3±1 (range 1-7) years.

Happiness with sexual function and the reassignment surgery was reported to be lower when permanent vaginal stenosis, clitoral necrosis, pain in the vagina or genitals, or other complications such as infection, bleeding, poor healing, other tissue loss, other tissue necrosis, urinary incontinence, and genital numbness were present. Quality-of-life (QOL) was impaired when pain in the vagina or genitals was present.

Satisfaction with sexual function, gender reassignment surgery, and overall QOL was lower when genital sensation was impaired and when vaginal architecture and lubrication were perceived to be unsatisfactory. Intermittent regret regarding reassignment surgery was associated with vaginal hair and clitoral pain. Vaginal stenosis was associated with surgeries performed longer ago; whereas, more satisfaction with vaginal depth and width was present in more recent surgeries.

f. <u>Prospective, non-blinded, observational, longitudinal and patients served as their own controls</u>

Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. J Sex Med. 2014 Jan;11(1):119-26. Epub 2013 Oct 28.

Heylens et al. conducted a prospective, non-blinded observational study using a longitudinal design in which patients served as their own controls. They used a non-specific psychiatric test with normative data along with two self-designed questionnaires. The investigators assessed psychosocial adjustment and psychopathology in patients with gender identity disorders. Patients were to be sequentially evaluated prior to institution of hormonal therapy, then 3 to 6 months after the start of cross-sex hormone treatment, and then again one to 12 months after reassignment surgery. The Dutch version of the SCL-90R with 8 subscales (agorophobia, anxiety, depression, hostility, interpersonal sensitivity, paranoid ideation/psychoticism, and sleeping problems) and a global score (psycho-neuroticism) was used serially. A seven parameter questionnaire was used serially to assess changes in social function. Another cross-sectional survey assessed emotional state. The cohorts at each time point consisted of patients who were in the treatment cohort at the time and who had submitted survey responses.

Ninety of the patients who applied for reassignment surgery between June 2005 and March 2009 were recruited. Fifty seven entered the study. Forty six (51.1% of the recruited population) underwent reassignment surgery. Baseline questionnaire information was missing for 3 patients. Baseline SCL-90 scores were missing for 1 patient but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. Time point 2 (after hormone therapy) SCL-90 information was missing for 10, but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. At time point 3, 42 (91.3% of those who underwent reassignment surgery) patients completed some part of the SCL-90 survey and the psychosocial questionnaires. Some questionnaires were incomplete. The investigators reported response rates of 73.7% for the psychosocial questionnaires and 82.5% rates the SCL-90.

Of those who responded at follow-up after surgery, 88.1% reported having good friends; 52.4% reported the absence of a relationship; 47.6% had no sexual contacts; 42.9% lived alone; 40.5% were unemployed, retired, students, or otherwise not working; 2.4% reported alcohol abuse; and 9.3% had attempted suicide. The frequency of these parameters reportedly did not change statistically during the study interval, but there was no adjustment for

the inclusion of patients who did not undergo surgery.

In a cross-sectional, self-report mood survey, of the 42 study entrants who completed the entire treatment regimen including reassignment surgery and the final assessment (refers to the initial 57) reported improved body-related experience (97.6%), happiness (92.9%), mood (95.2%), and self-confidence (78.6%) and reduced anxiety (81.0%). Of participants, 16.7% reported thoughts of suicide. Patients also reported on the intervention phase that they believed was most helpful: hormone initiation (57.9%), reassignment surgery (31.6%), and diagnostic-psychotherapy phase (10.5%).

The global "psycho-neuroticism" SCL-90R score, along with scores of 7 of the 8 subscales, at baseline were statistically more pathologic than the general population. After hormone therapy, the score for global "psycho-neuroticism" normalized and remained normal after reassignment surgery. More specifically the range for the global score is 90 to 450 with higher scores being more pathologic. The score for the general population was 118.3±32.4. The respective scores for the various gender dysphoric cohorts were 157.7±49.8 at initial presentation, 119.7±32.1 after hormone therapy, and 127.9±37.2 after surgery. The scores for the general population and the scores after either hormone treatment or surgical treatment did not differ.

Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med. 2005 Jan;35(1):89-99.

Smith et al. conducted a prospective, non-blinded, observational study using a longitudinal design and psychological function tools. Patients served as their own control prior to and after reassignment surgery. The investigator assessed gender dysphoria, body dissatisfaction, physical appearance, psychopathology, personality traits, and post-operative function in patients with gender dysphoria. Patients underwent some aspect of reassignment surgery. The test instruments included the Utrecht Gender Dysphoria Scale (12 items), the Body Image Scale adapted for a Dutch population (30 items), Appraisal of Appearance Inventory (3 observers, 14 items), the Dutch Short MMPI (83 items), the Dutch version of the Symptom Checklist (SCL)(90 items), and clinic-developed or modified questionnaires. Pre-treatment data was obtained shortly after the initial interview. Post-surgery data were acquired at least 1 year post reassignment surgery.

The size of the pool of available patients was not identified. Overall 325 consecutive adolescents and adults initially were "involved." Of these, 103 (29 [28.2%] female-to-male patients and 74 [71.8%] male-to-female patients [ratio 1:2.6]) never started hormone therapy; 222 (76 [34.2%] female-to-male patients and 146 [65.8%] male-to-female patients [ratio 1:1.9]) initiated hormone therapy. Of the patients who started hormone therapy, 34 (5 [14.7%] female-to-male patients and 29 [85.3%] male-to-female patients [ratio 1:5.8]) discontinued hormone therapy. After discontinuation of hormone therapy, the study was limited to adults. Of adults, 162 (58 [35.8%] female-to-male and 104 [64.2%] male-to-female [ratio 1:1.8]) were eligible and provided pre-surgical test data, and 126 (77.8% of eligible adults) (49 [38.9%] female-to-male and 77 [61.1%] male-to-female [ratio 1:1.6]) provided post-surgical data. For those patients who completed reassignment, the mean age at the time of surgical request was 30.9 years (range 17.7-68.1) and 35.2 years (range 21.3-71.9) years at the time of follow-up. The intervals between hormone treatment initiation and surgery and surgery and follow-up were 20.4 months (range 12 to 73) and 21.3 months (range 12 to 47) respectively.

Of the 126 adults who provided post-surgical data, 50 (40.0%) reported having a steady sexual partner, three (2.3%) were retired, and 58 (46.0%) were unemployed. Regarding regret, six patients expressed some regret regarding surgery, but did not want to resume their natal gender role, and one male-to-female had significant regret and would not make the same decision.

Post-surgery Utrecht dysphoria scores dropped substantially and approached reportedly normal values. The patients'

appearance better matched their new gender. No one was dissatisfied with his/her overall appearance at follow-up. Satisfaction with primary sexual, secondary sexual, and non-sexual body traits improved over time. Male-to-female patients, however, were more dissatisfied with the appearance of primary sex traits than female-to-male patients. Regarding mastectomy, 27 of 38 (71.1%) female-to-male respondents (not including 11 non-respondents) reported incomplete satisfaction with their mastectomy procedure. For five of these patients, the incomplete satisfaction was because of scarring. Regarding vaginoplastly, 20 of 67 (29.8%) male-to-female respondents (not including 10 non-respondents) reported incomplete satisfaction with their vaginoplasty.

Most of the MMPI scales were already in the normal range at the time of initial testing. SCL global scores for psycho-neuroticism were minimally elevated before surgery 143.0±40.7 (scoring range 90 to 450) and normalized after surgery 120.3±31.4. (An analysis using patient level data for only the completers was not conducted.)

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. Sexual and Relationship Therapy. 2007 Feb; 22(1):77-81. (Not in PubMed) and *Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. Sexual and Relationship Therapy. 2008 May; 23(2):141-5. (Not in PubMed)*

Udeze et al. conducted a prospective, non-blinded, longitudinal study assessing a randomized subset of patients who had completed a non-specific psychological function tool prior to and after male-to-female reassignment surgery. Patients served as their own controls. The investigators used the WPATH criteria for patient selection. Psychiatric evaluations were routine. All patients selected for treatment were routinely asked to complete the self-administered SCL-90R voluntarily on admission to the program and post-operatively. A post-operative evaluations (psychiatric and SCL-90R assessment) were conducted within 6 months to minimize previously determined loss rates. The patient pool was domestic and international. There were 546 gender dysphoric patients from all over the United Kingdom and abroad, of whom 318 (58.2%) progressed to surgery. Of these, 127 were from the local Leicester area in the United Kingdom and 38 (29.9%) progressed to surgery. The mean age for the selected male-to-female patients at the time of study was 47.33±13.26 years (range 25 to 80) and reflected an average wait time for surgery of 14 months (range 2 months to 6 years). For this investigation, 40 male-to-female subjects were prospectively selected.

The raw SCL-90 global scores for psycho-neuroticism were unchanged over time: 48.33 prior to surgery and 49.15 after surgery. If the scale was consistent with T-scoring, the results were non-pathologic. A statistical trend in the anger/hostility subscale was reported. No psychiatric disorders were otherwise identified prior to or after surgery.

Investigators from the same clinical group (Megeri, Khoosal, 2007) conducted additional testing to specifically address anxiety and depression with the Beck Depression Inventory, General Health Questionnaire (with 4 subscales), HADS, and Spielberger State and Trait Anxiety Questionnaire (STAI-X1 and STA-X2). The test population and study design appear to be the same. No absolute data were presented. Only changes in scores were presented. There were no statistically significant changes.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. Arch Sex Behav. 1987 Dec;16(6):511-22.

Kockott and Fahrner conducted a prospective, observational study using a longitudinal design. Treatment cohorts were used as controls, and patients served as their own controls. The investigators assessed psychosocial adjustment in patients with gender identity issues. Patients were to have met DSM III criteria. Trans-sexuality, transvestitism, and homosexuality were differentiated. The criteria required for patients to receive hormone therapy and/or reassignment surgery were not delineated. After receiving hormone therapy, patients were later classified by surgical reassignment status (pre-operative and post-operative) and desire for surgery (unchanged desire, hesitant, and no longer desired).

The first investigative tool was a semi-structured in-person interview consisting of 125 questions. The second investigative tool was a scale that organized the clinical material into nine domains which were then scored on a scale. The Psychological Integration of Trans-sexuals (PIT) instrument was not otherwise described in the publication or in other citations. There were 15 interviews and two separate interviewers. There were 80 patients identified, but 58 (72.5%) patients (26 pre-operative; 32 post-operative) were ultimately included in the analysis. The duration of follow-up was longer for post-operative patients (6.5 years) than for pre-operative patients (4.6 years) (including time for one patient subsequently excluded). The mean age of the post-operative patients was 35.5±13.1 years, and the age of the patients who maintained a continued desire for surgery was 31.7±10.2 years. The age of the patients who hesitated about surgery was somewhat older, 40.3±9.4 years. The age of the patients who were no longer interested in surgery was 31.8±6.5 years. All were employed or in school at baseline. Patients with hesitation were financially better-off, had longer-standing relationships even if unhappy, and had a statistical tendency to place less value on sex than those with an unchanged wish for surgery.

Post-operative patients more frequently reported contentment with the desired gender and the success of adaption to the gender role than the pre-operative patients with a persistent desire for surgery. Post-operative patients more frequently reported sexual satisfaction than pre-operative patients with a continuing desire for surgery. Post-operative patients also more frequently reported financial sufficiency and employment than pre-operative patients with a persistent desire for surgery. Suicide attempts were stated to be statistically less frequent in the post-surgical cohort.

Psychosocial adjustment scores were in the low end of the range with "distinct difficulties" (19-27) at the initial evaluation for the post-operative patients (19.7), the pre-operative patients with a persistent wish for surgery (20.2), and the hesitant patients (19.7). At initial evaluation, psychosocial adjustment scores for patients no longer wanting surgery were at the high end of the range with "few difficulties" (10-18). At the final evaluation, Psychosocial adjustment scores were at the high end of the range "few difficulties" (10-18) for the post-operative patients (13.2) and the patients no longer wanting surgery (16.5). Psychosocial adjustment scores at the final evaluation were in the borderline range between "few difficulties" (10-18) and "distinct difficulties" (19-27) for both the pre-operative patients with a persistent desire for surgery (18.7), and the hesitant patients (19.1).

The changes in the initial score and the final follow-up score *within e*ach group were tracked and reported to be statistically significant for the post-operative group, but not for the other groups. Statistical differences *between* groups were not presented. Moreover, the post-operative patients had an additional test immediately prior to surgery. The first baseline score (19.7) would have characterized the patients as having "distinct difficulties" in psychosocial adjustment while the second baseline score (16.7) would have categorized the patients as having "few difficulties" in psychosocial adjustment despite the absence of any intervention except the prospect of having imminent reassignment surgery. No statistics reporting on the change between scores of the initial test and the test immediately prior to surgery and the change between scores of the test immediately prior to surgery and the final follow-up were provided.

g. <u>Prospective, non-blinded, observational, longitudinal study with retrospective baseline data</u>

Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry. 1979 Aug;36(9):1010-5. (United States study)

Meyer and Reter conducted a prospective, non-blinded, observational study using a longitudinal design and retrospective baseline data. Interview data were scored with a self-designed tool. There were treatment control cohorts, and patients served as their own controls. The investigators assessed patients with gender dysphoria. The 1971 criteria for surgery required documented cross-sex hormone use as well as living and working in the desired gender for at least 1 year in patients subsequently applying for surgery. Clinical data including initial interviews were

used for baseline data. In follow-up, the investigators used extensive 2 to 4 hour interviews to collect information on (a) objective criteria of adaptation, (b) familial relationships and coping with life milestones, and (c) sexual activities and fantasies. The objective criteria, which were the subject of the publication, included employment status (Hollingshead job level), cohabitation patterns, and need for psychiatric intervention. The investigators designed a scoring mechanism for these criteria and used it to determine a global adjustment score.

The clinic opened with 100 patients, but in follow-up, 52 of the 100 patients were interviewed and 50 of the interviewees gave consent for publication. Of these, 15 (4 female-to-male, 11 male-to-female; ratio 1:2.8) were part of the initial operative cohort, 14 (1 female-to-male; 13 male-to-female; ratio 1:13) later underwent reassignment surgery at the institution or elsewhere, and 21 (5 female-to-male; 16 male-to-female; ratio 1:3.2) did not undergo surgery. The mean ages of these cohorts were 30.1, 30.9, and 26.7 years respectively. The mean follow-up time was 62 months (range 19-142) for those who underwent surgery and 25 months (range 15-48) for those who did not. Socioeconomic status was lowest in those who subsequently underwent reassignment surgery.

Of patients initially receiving surgery, 8% had some type of later psychiatric contact, which was approximately 3.5 times higher in those who had not under gone surgery or who had done so later. There was a single female-to-male patient with multiple surgical complications who sought partial reassignment surgery reversal.

The adjustment scores improved over time with borderline statistical significance for the initial operative group and with statistical significance for the never operated group. Both the absolute score value at follow-up and the magnitude of change were the same. By contrast, the adjustment scores did not improve for those who were not in the cohort initially approved for surgery, but who subsequently underwent surgery later. This was particularly true if the surgery was performed elsewhere.

h. <u>Prospective, non-blinded, observational, semi-cross sectional with no controls</u>

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav. 2010 Dec;39(6):1429-37. Epub 2009 Oct 9.

Johansson et al. conducted non-blinded, observational study using a semi-cross-sectional design (albeit over an extended time interval) using a self-designed tool and Axis V assessment. The study was prospective except for the acquisition of baseline Axis V data. There were no formal controls in this mixed population with and without surgery.

The investigators assessed satisfaction with the reassignment process, employment, partnership, sexual function, mental health, and global satisfaction in gender-reassigned persons from two disparate geographic regions. No other information regarding the sites of care was provided. Surgical candidates were required to have met National Board of Health and Welfare criteria including initial and periodic psychiatric assessment, ≥1 year of real-life experience in preferred gender, and ≥1 year of subsequent hormone treatment. In addition, participants were required to have been approved for reassignment 5 or more years prior and/or to have completed surgical reassignment (e.g., sterilization, genital surgery) 2 or more years prior. The investigators employed semi-structured interviews covering a self-designed list of 55 pre-formulated questions with a 3 or 5 point ordinal scale. Clinician assessment of Global Assessment of Functioning (GAF; Axis V) was also conducted and compared to initial finding during the study. Changes or differences considered to be biologically significant were not pre-specified. Diagnostic cut points were not provided. Statistical corrections for multiple comparisons were not included. There was no stratification by treatment.

Of the pool of 60 eligible patients, there were 21 (35.0%) female-to-male and 39 (65%) male-to-female (ratio 1:1.9) ; 32 (53.3% of eligible) (14 [43.8%] female-to-male; 18 [56.2%] male-to-female [ratio 1:1.3]) had completed genital gender reassignment surgery (not including 1 post mastectomy), 5 were still in the process of completing surgery, and 5 (1 female-to-male; 4 male-to-female; ratio 1:4) had discontinued the surgical process prior to

castration and genital surgery.

The ages of the patients (ranges) at entry into the program, reassignment surgery, and follow-up were 27.8 (18-46), 31.4 (22-49), and 38.9 (28-53) in the female-to-male group respectively and 37.3 (21-60), 38.2 (22-57), and 46.0 (25.0-69.0) in the male-to-female group respectively. The differences in age by cohort group were statistically significant. Of participants, 88.2% of all enrolled female-to-male versus 44.0% of all enrolled female-to-male patients had cross-gender identification in childhood (versus during or after puberty) ($p<0.01$).

Although 95.2% of all enrolled patients self-reported improvement in GAF, in contrast, clinicians determined GAF improvement in 61.9% of patients. Clinicians observed improvement in 47% of female-to-male patients and 72% of male-to-female patients. A ≥5 point improvement in the GAF score was present in 18 (42.9%). Of note, three of the five patients who were in the process of reassignment and five of the five who had discontinued the process were rated by clinicians as having improved.

Of all enrolled 95.2% (with and without surgery) reported satisfaction with the reassignment process. Of these patients, 33 (79%) identified themselves by their preferred gender and nine (21%) identified themselves as transgender. None of these nine (eight male-to-female) had completed reassignment surgery because of ambivalence secondary to lack of acceptance by others and dissatisfaction with their appearance. Of the patients who underwent genital surgery (n=32) and mastectomy only (n=1), 22 (66.7%) were satisfied while four (three female-to-male) were dissatisfied with the surgical treatment.

Regarding relationships after surgery, 16 (38%) (41% of female- to-male; 36% of male-to-female) were reported to have a partner. Yet more than that number commented on partner relationships: 62.2 % of the 37 who answered (50.0% of female- to-male; 69.6% of male-to-female) reported improved partner relationships (5 [11.9%] declined to answer.); 70.0% of the 40 who answered (75.0% of female-to-male; 66.7% of male-to-female) reported an improved sex life. Investigators observed that reported post-operative satisfaction with sex life was statistically more likely in those with early rather than late cross-gender identification.

In addition 55.4% self-reported improved general health; 16.1% reported impaired general health; 11.9% were currently being treated with anti-depressants or tranquilizers; 44.7 % of the 38 who answered (53.3% of female-to-male; 39.1% of male-to-female) reported improved work circumstances (4 [9.5%] declined to answer.); 61.9% were students or employed. The remainder (38.1%) were living on disability pensions (28.6%), unemployed (4.8%), or retired (4.8%).

i. <u>Prospective, cross sectional, observational, internet self- report survey, with unknown blinding, no formal controls</u>

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. Qual Life Res. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. (United States study)

Newfield et al. conducted a prospective, observational internet self-report survey of unknown blinding status using a cross-sectional design and a non-specific quality of life tool in a mixed, population with and without reassignment surgery. There were no formal controls.

The investigators recruited natal female participants identifying as male using email, internet bulletin boards, and flyers/postcards distributed in the San Francisco Bay Area. Reduction of duplicate entries by the same participant was limited to the use of a unique user name and password.

The investigators employed the SF-36 Version 2 using U.S. normative data. They reported using both male and female normative data for the comparator SF-36 cohort. Data for the 8 domains were expressed as normative scoring. The Bonferroni correction was used to adjust for the risk of a Type 1 error with analyses using multiple comparisons.

A total of 379 U.S. respondents classified themselves as males or females to males with or without therapeutic intervention. The mean age of the respondents who classified themselves as male or female-to-male was 32.6±10.8 years. 89% were Caucasian, 3.6% Latino, 1.8% African American, 1.8% Asian, and 3.8% other. 254 (67.0%) reported any testosterone use in the past or currently; and 242 (63.8%) reported current testosterone use. In addition, 136 (36.7%) reported having had "top" surgery and 11 (2.9%) reported having "bottom" surgery. The Physical Summary Score (53.45±9.42) was statistically higher (better) than the natal gender unspecified SF-36 normative score (50±10) (p=<0.001), but was within 1 standard deviation of the normative mean. The Mental Summary Score (39.63±12.2) was statistically lower (worse) than the natal gender unspecified SF-36 normative score (50±10) (p<0.001), but was well within 2 standard deviations of the normative mean. Subcomponents of this score: Mental Health (42.12±10.2), Role Emotional (42.42±11.6), Social Functioning (43.14±10.9), and Vitality (46.22±9.9) were statistically lower (worse) than the SF-36 normative sub-scores, but well within 1 standard deviation of the normative sub-score means. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

Additional intragroup analyses were conducted, although the data were not stratified by type of therapeutic intervention (hormonal, as well as, surgical). Outcomes of hormone therapy were considered separately and dichotomously from reassignment surgery. The Mental Summary Score was statistically higher (better) in those who had "Ever Received Testosterone" (41.22±11.9) than those with "No Testosterone Usage" (36.08±12.6) (p=0.001). The Mental Summary Scores showed a trend towards statistical difference between those who "Ever Received Top Surgery" (41.21±11.6) and those without "Top Surgery" (38.01±12.5) (p=0.067). These differences were well within 1 standard deviation of the normative mean. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

j. <u>Partially prospective, non-blinded, observational studies with longitudinal designs and patients served as their own controls</u>

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. Arch Sex Behav. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18.

Ruppin and Pfafflin conducted a partially prospective, non-blinded, observational study using a longitudinal design and non-specific psychometric tests and a self-designed interview tool and questionnaire. Patients served as their own controls.

The investigators assessed psychological symptoms, interpersonal difficulties, gender role stereotypes, personality characteristics, societal function, sexual function, and satisfaction with new gender role in patients with gender dysphoria. Patients were required to have met the ICD-10 criteria for trans-sexualism, been seen by the clinic by prior to 2001, and completed an official change in gender including name change prior to 2001. Assessment tools included German versions of standardized surveys with normative data: the SCL 90R, the Inventory of Interpersonal Problems (IIP), Bem Sex Role Inventory (BSRI), and the Freiburg Personality Inventory (FPI-R), along with semi-structured interviews with self-designed questionnaires. The prospective survey results were compared to retrospective survey results.

Overall, 140 patients received recruitment letters then 71 (50.7%) agreed to participate. Of these participants, 36 (50.7%) were female-to-male; 35 (49.3%) were male-to-female (ratio 1:0.97). The ages of the patients were:

41.2±5.78 years female-to-male and 52.9±10.82 years male-to-female 52.9±10.82 years. The intervals for follow-up were 14.1±1.97 years and 13.7±2.17 years respectively.

All female-to-male patients had undergone mastectomy; 91.7% had undergone oopherectomy and/or hysterectomy; 61.1% had undergone radial forearm flap phalloplasty or metaoidioplasty; 94.3% of male-to-female patients had undergone vaginoplasty and perhaps an additional procedure (breast amplification, larynx surgery, or vocal cord surgery). Two male-to-female patients had not undergone any reassignment surgery, but were still included in the analyses.

A total of 68 patients ranked their well-being as 4.35±0.86 out of five (three patients did not respond to this question). Of respondents, 40% reported not in a steady relationship. Regular sexual relationships were reported by 57.1% of 35/36 female-to-male respondents and 39.4% of 33/35 of male-to-female respondents (three patients did not respond to this question). A total of 11 patients reported receiving out-patient psychotherapy; 69 did not express a desire for gender role reversal (two did not respond to this question). The response rate was less than 100% for most of the self-designed survey questions.

Changes from the initial visit to the follow-up visit were assessed for the SCL-90R in 62 of 71 patients. Changes from the initial visit to the follow-up visit were assessed for the IIP in 55 of 71 patients. Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 58 of 71 patients. The effect size was large only for the "Life Satisfaction" scale. Changes from the initial visit to the follow-up visit were assessed for the BSRI in 16 of 36 female-to-male patients and 19 of 35 male-to-female patients. The "Social Desirability" score increased for the female-to-male respondents. At endpoint, both categories of respondents reported androgynous self-images.

k. <u>Partially prospective, non-blinded, observational studies with cross-sectional designs that had control groups but were not concurrent</u>

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand. 2000 Oct;102(4):276-81.

Haraldsen and Dahl conducted a partially prospective, non-blinded, observational study using a cross-sectional design and a non-specific psychometric test. There was a control group, but it was not concurrent.

In the germane sub-study, the investigator assessed psychopathology in patients with gender dysphoria. Patients, who were independently evaluated by 2 senior psychiatrists, were required to meet DSM III-R or DSM IV diagnostic criteria and the Swedish criteria for reassignment surgery. The Norwegian version of the SCL-90 was used. The testing was conducted from 1987 to 1989 for those who had undergone reassignment surgery between 1963 and 1987 and from 1996 to 1998 for pre-surgical patients who had applied for reassignment surgery between 1996 and 1998. In addition, Axis I, Axis II, and Axis V (Global Functioning) was assessed.

Of 65 post–surgical and 34 pre-surgical patients, 59 post-surgical and 27 pre-surgical patients ultimately entered the study. The combined cohorts consisted of 35 (40.7%) female-to-male patients and 51 (59.3%) male-to-female patients (ratio 1:1.5). The ages were female-to-male 34±9.5 years and female-to-male 33.3±10.0 years. The other control group consisted of patients with personality disorder. 101 (27 men (33.9±7.3 years) and 74 women (31.6±8.2) were tested during a treatment program. One year later, 98% were evaluated.

A total of 28 (32.5%) of the pre- and post- reassignment surgery patients had an Axis I diagnosis compared to 100 (99.0%) of those with personality disorders. Depression and anxiety were the most common diagnoses in both groups, but were approximately three to four times more common in the personality disorder cohort. Seventeen

(19.8%) of the pre- and post- reassignment surgery patients had an Axis II diagnosis whereas the mean number of personality disorders in the personality disorder cohort was 1.7±1. The Global Assessment of Function was higher (better) in the gender dysphoric groups 78.0±8.9 than in the personality disorder cohort (53.0±9.0).

Global Severity Indices (GSI) were highest for those with personality disorder regardless of gender and exceeded the cut-point score of 1.0. The GSI scores for females-to-males and males-to-females were 0.67±57 and 0.56±0.45. Although they were nominally higher than the healthy normative controls (males: 0.32±0.36 and females 0.41±0.43), they were well within the non-pathologic range. The same was true for the subscales.

SCL-90 GSI scores did not differ substantively between pre- and post-surgical patients, nor did the SCI subscale scores differ substantively between pre- and post-surgical patients. Any small non-significant differences tracked with the age and sex differences.

I. <u>Partially prospective, non-blinded, observational studies with cross-sectional designs that had no control groups</u>

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. Endocr Pract. 2013 Jul-Aug;19(4):644-50. (United States study)

Leinung et al. conducted a partially prospective, non-blinded, observational study using a cross-sectional design and descriptive statistics. There were no formal controls. The investigators assessed employment, substance abuse, psychiatric disease, mood disorders, Human Immunodeficiency Virus (HIV) status in patients who had met WPATH guidelines for therapy, and who had initiated cross-sex hormone treatment.

A total of 242 patients treated for gender identity disorder in the clinic from 1992 through 2009 inclusive were identified. The number of those presenting for therapy almost tripled over time. Of these patients, 50 (20.7%) were female-to-male; 192 (79.3%) male-to-female (ratio 1:3.8).

The age of female-to-male and male-to-female patients with gender dysphoria at the time of clinic presentation was 29.0 and 38.0 years respectively.

The female-to-male and male-to-female patients with gender dysphoria at the time of hormone initiation were young: 27.5 and 35.5 years old respectively ($p<0.5$). Of the male-to-female cohort, 19 (7.8%) had received hormone therapy in the absence of physician supervision; 91 (37.6%) had undergone gender-reassignment surgery (32 female-to-male [64.0% of all female-to-male; 35.2% of all surgical patients]; 59 male-to-female [30.7% of all male-to-female; 64.8% of all surgical patients]; ratio 1:1.8).

Psychiatric disease was more common in those who initiated hormone therapy at an older age (>32 years) 63.9% versus 48.9% at a younger age and by natal gender (48.0% of female-to-male; 58.3% male-to-female). Mood disorders were more common in those who initiated hormone therapy at an older age (>32 years) 52.1% versus 36.0% at a younger age and this finding did not differ by natal gender (40.0% of female-to-male; 44.8% male-to-female). The presence of mood disorders increased the time to reassignment surgery in male-to-female patients. Of participants 36.4% were employed in jobs requiring a high school degree or less; 28.1% (excluding students) were on disability and/or unemployed. Rates of disability and unemployment were higher in male-to-female patients (31.8%) than female-to-male patients (14.0%). Mental health diagnoses reportedly were the major reason for disability. HIV infection and substance abuse were higher in male-to-female patients than female-to-male patients (8.3% versus 0% and 12.5% versus 6.0% respectively).

m. <u>Retrospective, non-blinded, observational, longitudinal studies</u>

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011 Apr;164(4):635-42. Epub 2011 Jan 25.

Asscheman et al. conducted a retrospective, non-blinded, observational study of mortality using a longitudinal design of population treated with hormones, as well as, reassignment surgery and a population-based cohort. The investigators assessed mortality in patients who (a) were from a single-center, unspecified, university specialty clinic, (b) initiated cross-sex hormone treatment prior to July 1, 1997, and (c) had been followed by the clinic for at least 1 year or had expired during the first year of treatment. The National Civil Record Registry (Gemeentelijke Basis Administratie) was used to identify/confirm deaths of clinic patients. Information on the types or hormones used was extracted from clinic records, and information on the causation of death was extracted from medical records or obtained from family physicians. Mortality data for the general population was obtained through by the Central Bureau of Statistics of the Netherlands. Mortality data from Acquired Immune Deficiency Syndrome (AIDS) and substance abuse were extracted from selected Statistics Netherlands reports. The gender of the general Dutch population comparator group was the natal sex of the respective gender dysphoric patient groups.

A total of 1,331 patients who met the hormone treatment requirements were identified (365 female-to-male [27.4%]; 966 male-to-female [72.6%]; ratio 1:2.6). Of these, 1,177 (88.4%) underwent reassignment surgery (343 [94.0% of female-to-male entrants]; 834 [86.3% of male-to-female entrants]; ratio 1:2.4; p<0.0001). The mean age at the time of hormone initiation in female-to-male and male-to-female patients was young: 26.1±7.6 (range 16–56) years and 31.4±11.4 (range 16–76) years respectively, although the male-to-female subjects were relatively older (p<0.001). The mean duration of hormone therapy in female-to-male and male-to-female patients was 18.8±6.3 and 19.4±7.7 years respectively.

There were a total of 134 deaths in the clinic population using hormone therapy as well as reassignment surgery. Of the patients, 12 (3.3%) of the 365 female-to-male patients and 122 (12.6%) of the 966 male-to-female patients died. All-cause mortality was 51% higher and statistically significant (Standardized Mortality Ratio [SMR] 95% confidence interval [CI]) 1.47-1.55) for males-to-females when compared to females in the general Dutch population. The small increase in all-cause mortality (12%) for females-to-males when compared to males in the general Dutch population was not statistically significant; 95% CI 0.87-1.42.

The major known contributors to the mortality difference between male-to-female patients and the Dutch population at large were completed suicide (n=17, SMR 5.70 [95% CI 4.93-6.54]), AIDS (n=16, SMR 30.20 [95% CI 26.0-34.7), and illicit drug use (n=5, SMR 13.20 [95% CI 9.70-17.6]). An additional major contributor was "unknown cause" (n=21, SMR 4.00 [95% CI 3.52-4.51]). Of the 17 male-to-female hormone treated patients who committed suicide, 13 (76.5%) had received prior psychiatric treatment and 6 (35.3%) had not undergone reassignment surgery because of concerns about metal health stability.

Ischemic heart disease was a major disparate contributor to excess mortality in male-to-female patients in older patients (n=18, SMR 1.64 [95% CI 1.43-1.87], mean age [range]: 59.7 [42-79] years. Current use of aparticular type of estrogen, ethinyl estradiol, was found to contribute to death from myocardial infarction or stroke (Adjusted Hazard Ratio 3.12 [95% CI 1.28-7.63), p=0.01). There was a smaller, but statistically significant increase in lung cancer that was thought to possibly be related to higher rates of smoking in this cohort.

Although overall mortality was not increased in the hormone-treated female-to-male patients, there were more deaths due to illicit drug use than expected (SMR 25 [6.00-32.5]).

n. <u>Retrospective, non-blinded, observational, longitudinal studies using matched national data</u>

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One. 2011;6(2):e16885. Epub 2011 Feb 22.

Dhejne et al. conducted a retrospective, non-blinded, observational study of nation-wide mortality using a longitudinal and a population-based matched cohort. The investigators assessed mortality, suicide attempts, psychiatric hospitalization, and substance abuse in gender-reassigned persons and randomly selected unexposed controls matched by birth year and natal sex (1:10) as well as by birth year and the reassigned gender (1:10). Data were extracted from national databases including the Total Population Register (Statistics Sweden), the Medical Birth Register, the Cause of Death Register (Statistics Sweden), the Hospital Discharge Register (National Board of Health and Welfare), the Crime Register (National Council of Crime), and those from the Register of Education for highest educational level. The criteria required to obtain the initial certificate for reassignment surgery and change in legal status from the National Board of Health and Welfare were not delineated, but included evaluation and treatment by one of 6 specialized teams, name change, a new national identity number, continued use of hormones, and sterilization/castration. Descriptive statistics with hazard ratios were provided. There were 804 patients identified with gender identity disorder (or related disorder) in Sweden during the period from 1973 to 2003 inclusive. Of these patients, 324 (40.3%) underwent gender-reassignment surgery (133 female-to-male [41.0%]; 191 male-to-female [59.0%]; ratio 1:1.4). The average follow-up time for all-cause mortality was 11.4 years (median 9.1). The average follow-up time for psychiatric hospitalization was 10.4 years (median 8.1).

The mean ages in female-to-male and male-to-female reassigned patients were: 33.3±8.7 (range 20–62) and 36.3± 10.1 (range 21–69) respectively. Immigrant status was two times higher in reassigned patients (n=70, 21.6%) than in either type of control (birth [natal] sex matched n=294 [9.1%] or reassigned gender matched n=264 [8.1%]). Educational attainment (10 or more years) was somewhat lower for reassigned patients (n=151 [57.8%]) than in either type of control (birth sex matched n=1,725 [61.5%] or reassigned gender matched n=1804 [64.3%]) (cohort data were incomplete). The biggest discordance in educational attainment was for female-to-male reassigned patients regardless of the control used. Prior psychiatric morbidity (which did not include hospitalization for gender dysphoria) was more than four times higher in reassigned patients (n=58, 17.9%) than in either type of control (birth sex matched n=123 [3.8%] or reassigned gender matched n=114 [3.5%]).

All-cause mortality was higher for patients who underwent gender reassignment surgery (n=27 [8.3%]) than in controls (hazard ratio 2.8 [1.8-4.3]) even after adjustment for covariants (prior psychiatric morbidity and immigration status). Divergence in the survival curves began at 10 years. The major contributor to this mortality difference was completed suicide (n=10 [3.1%]; adjusted hazard ratio 19.1 [5.8-62.9]). Mortality due to cardiovascular disease was modestly higher for reassigned patients (n=9 [2.8%]) than in controls (hazard ratio 2.5 [1.2-5.3]).

Suicide attempts were more common in patients who underwent gender reassignment surgery (n= 29 [9.0%] than in controls (adjusted hazard ratio 4.9 [2.9–8.5]). Male- to-female patients were at higher adjusted risk for attempted suicide than either control whereas female-to-male patients were at higher adjusted risk compared to only male controls and maintained the female pattern of higher attempted suicide risk. Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common in reassigned persons n= 64 [20.0%] than in controls (hazard ratio 2.8 [2.0–3.9]) even after adjusting for prior psychiatric morbidity. Hospitalization for substance abuse was not greater than either type of control. The increased risk for conviction of any crime or violent crime observed during the 1973-1988 interval was not seen later.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-

2010: prevalence, incidence, and regrets. Arch Sex Behav. 2014 Nov;43(8):1535-45. Epub 2014 May 29 and Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand. 1998 Apr;97(4):284 (Dhejne et al., 2014; Landen et al., 1998) Sweden-All

Dhejne et al. conducted a non-blinded, observational study that was longitudinal for the capture of patients with "regret" in a national database. This same group (Landen et al., 1998) conducted a similar study along with retrospective acquisition of clinical data to explore the differences between the cohorts with and without regret. There were no external controls; only intra-group comparisons for this surgical series.

The investigators assessed the frequency of regret for gender reassignment surgery. Data were extracted from registries at the National Board of Health and Welfare to which patients seeking reassignment surgery or reversal of reassignment surgery make a formal application and which has maintained such records since a 1972 law regulating surgical and legal sex reassignment. The investigators reviewed application files from 1960 through 2010. The specific criteria to qualify for gender surgery were not delineated. Patients typically underwent diagnostic evaluation for at least 1 year. Diagnostic evaluation was typically followed by the initiation of gender confirmation treatment including hormonal therapy and real-life experience. After 2 years of evaluation and treatment, patients could make applications to the national board. Until recently sterilization or castration were the required minimal surgical procedures. (Dhejne et al., 2011) Secular changes in this program included consolidation of care to limited sites, changes in accepted diagnostic criteria, and provision of non-genital surgery, e.g., mastectomy during the real-life experience phase, and family support.

Of the 767 applicants for legal and surgical reassignment (289 [37.7%] female-to-male and 478 [62.3%] male-to-female; ratio 1:1.6]. The number of applicants doubled each ten year interval starting in 1981.

Of the applicants, 88.7% or 681 (252 [37.0%] female-to-male and 429 [63.0%] male-to-female; ratio 1:1.7] had undergone surgery and changed legal status by June 30, 2011. This number included eight (four [50.0%] female to-male and four [50.0%] male to female; ratio 1:1) people who underwent surgery prior to the 1972 law. (This number [6.0%] appears to include 41 (two [4.9%] female-to-male and 39 [95.1%] male-to-female; ratio 1:19.5) people who underwent surgery abroad at their own expense [usually in Thailand or the U.S.]. This cohort includes one person who was denied reassignment surgery by Sweden.)

Twenty-five (3.3%) of the applications were denied with the two most common reasons being an incomplete application or not meeting diagnostic criteria. An additional 61(8.0%) withdrew their application, were wait-listed for surgery, postponed surgery (perhaps in hopes of the later revocation of the sterilization requirement), or were granted partial treatment.

The formal application for reversal of the legal gender status, the "regret rate", was 2.2%. No one who underwent sex-reassignment surgery outside of Sweden (36 of 41 after 1991) has requested reversal. The authors noted, however, that this preliminary number may be low because the median time interval to reversal request was eight years-only three of which had elapsed by publication submission- and because it was the largest serial cohort. This number did not include other possible expressions of regret including suicide (Dhejne et al., 2011).

Dhejne et al. in 2014 reported that the female-to-male: male-to-female ratio among those who made formal applications for reversal was 1:2. The investigators also reported that the female-to-male applicants for reversal were younger than the entire female-to-male cohort (median age 22 versus 27 years) while the male-to-female applicants for reversal were older than the entire male-to-female cohort (median age 35 versus 32 years). Other clinical data to explore the differences between the cohorts with and without regret were not presented in this update publication.

In their earlier publication, in addition to determining a regret rate (3.8%), Landen et al. extracted data from medical records and government verdicts. Logistic regression analyses were used identify relationships between variables. They observed that: (a) 25.0% of the cohort with regrets and 11.4% of the cohort without regrets were unemployed, (b) 16.7% of the cohort with regrets and 15.4% of the cohort without regrets were on "sick benefit", (c) 15.4% of the cohort with regrets and 13.9% of the cohort without regrets had problems with substance abuse, (d) 69.2% of the cohort with regrets and 34.6% of the cohort without regrets had undergone psychiatric treatment, (e) 15.4% of the cohort with regrets and 8.8% of the cohort without regrets had a mood disorder, and (f) 15.4% of the cohort with regrets and 1.5% of the cohort without regrets had a psychotic disorder.

The putative prognostic factors that were statistically different (albeit without Bonferroni correction) between the cohorts with and without regret included prior psychiatric treatment, a history of psychotic disorder, atypical features of gender identity, and poor family support. Factors that trended towards statistical difference included having an unstable personality, sexual orientation and transvestitism. These variables were tested with logistic regression. Initial modeling included the variable "history of psychotic disorder". Although this variable was predictive, it was excluded from future analyses because it was already a contraindication to reassignment surgery. Additional analyses identified poor family support as the most predictive variable and atypical features of gender identity as the second most important variable. Presence of both variables has a more than additive effect.

The nationwide mortality studies by Dhejne et al. 2011 includes much, if not all, of the Landen (1998) patient population and most of the Dhejne (2014) population.

o. <u>Randomized, non-blinded, longitudinal, some patients served as their own controls</u>

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry. 1990 Aug;157:261-4.

Mate-Kole at al. conducted a prospective, non-blinded, controlled, randomized, longitudinal study using investigator-designed patient self-report questionnaires and non-specific psychological tests with some normative data. The investigators assessed neuroticism and sex role in natal males with gender dysphoria who had qualified for male-to-female reassignment surgery at a single-center specialty clinic. Forty sequential patients were alternately assigned to early reassignment surgery or to standard wait times for reassignment surgery. Patients were evaluated after acceptance and 2 years later. The criteria used to qualify for gender surgery were the 1985 standards from the Harry Benjamin International Gender Dysphoria Association. These included a ≥2 year desire to change gender, a ≥1 year demonstrable ability to live and be self-supporting in the chosen gender, and psychiatric assessment for diagnosis and reassessment at 6 months for diagnostic confirmation and exclusion of psychosis. Reassignment surgery was defined as orchidectomy, penectomy, and construction of a neo-vagina. The instruments used were the CCEI for psychoneurotic symptoms and the Bem Sex Role Inventory along with an incompletely described investigator-designed survey with questions about social life and sexual activity. The mean age and range of the entire cohort was 32.5 years (21-53).

Members of the early surgery cohort had a history of attempted suicide (one patient), psychiatric treatment for non-gender issues (six patients), and first degree relatives with psychiatric histories (four patients). Members of the standard surgery cohort were similar, with a history of attempted suicide (two patients), psychiatric treatment for non-gender issues (five patients), and first degree relatives with psychiatric histories (six patients). The early surgery group had surgery approximately 1.75 years prior to the follow-up evaluation. In both groups, cross-dressing began at about age 6.

At baseline, the Bem Sex Role Inventory femininity scores were slightly higher than masculinity scores for both cohorts and were similar to Bem North American female normative scores. The scores did not change in either group

over time.

At baseline, the scores for the CCEI individual domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were similar for the cohorts. The total CCEI scores for the two cohorts were consistent with moderate symptoms. Over the 2 year interval, total CCEI scores increased for standard wait group and approached the relatively severe symptom category. During the same interval, scores dropped into the asymptomatic rage for the post-operative patients.

The investigator-designed survey assessed changes in social and sexual activity of the prior 2 years, but the authors only compared patients in a given cohort to themselves. Though the researchers did not conduct statistical studies to compare the differences between the 2 cohorts, they did report increased participation in some, but not all, types of social activities such as sports (solo or group), dancing, dining out, visiting pubs, and visiting others. Sexual interest also increased. By contrast, pre-operative patients did not increase their participation in these activities. Work status remained the same for post-operative patients which unemployment increased in the standard wait pre-operative cohort.

2. External Technology Assessments

a. CMS did not request an external technology assessment (TA) on this issue.

b. There were no AHRQ reviews on this topic.

c. There are no Blue Cross/Blue Shield Health Technology Assessments written on this topic within the last three years.

d. There were two publications in the COCHRANE database, and both were tangentially related.

Both noted that there are gaps in the clinical evidence base for gender reassignment surgery.

Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations Boehmer U. *Am J Public Health*. 2002; 92: 1125–30.

"Findings supported that LGBT issues have been neglected by public health research and that research unrelated to sexually transmitted diseases is lacking."

A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. West Midlands Health Technology Assessment Collaboration. Health Technology Assessment Database. Meads, et al., 2009. No.3.

"Further research is needed but must use more sophisticated designs with comparison groups. This systematic review demonstrated that there are so many gaps in knowledge around LGBT health that a wide variety of studies are needed."

e. There were no National Institute for Health and Care Excellence (NICE) reviews/guidance documents on this topic.

f. There was a technology assessment commissioned by the New Zealand Ministry of Health and conducted by New

Zealand Health Technology Assessment (NZHTA) (Christchurch School of Medicine and the University of Otago).

Tech Brief Series: Transgender Re-assignment Surgery Day P*. NZHTA Report*. February 2002;1(1). *http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf*

The research questions included the following: (1) Are there particular subgroups of people with transsexualism who have met eligibility criteria for gender reassignment surgery (GRS) where evidence of effectiveness of that surgery exists? And (2) If there is evidence of effectiveness, what subgroups would benefit from GRS?" Based upon the research, "Some 593 possibly relevant articles in abstract form were identified of which 70 articles were retrieved in full text."

The NZHTA stated, "The reviewed studies may indicate that early, rather than delayed, sex reassignment surgery is of greater benefit to transsexual people who have gone through rigorous assessment procedures and have been accepted for surgery. Also, the reviewed studies identify characteristics of groups defined as core and non-core transsexual people, but these characteristics are heterogeneous and anecdotal."

The NZHTA also stated, "Gender reassignment surgery may benefit some carefully assessed and selected transsexual people who have satisfied recognized diagnostic and eligibility criteria, and have received recognized standards of care for surgery. More research is required to improve the evidence base identifying the subgroups of transsexual people most likely to benefit from sex reassignment surgery."

3. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) Meeting

CMS did not convene a MEDCAC meeting.

4. Evidence-Based Guidelines

a. American College of Obstetricians and Gynecologists (ACOG)

Though ACOG did not have any evidence-based guidelines on this topic, they did have the following document:

Health Care for Transgender Individuals: Committee Opinion

Committee on Health Care for Underserved Women; The American College of Obstetricians and Gynecologists. Dec 2011, No. 512. Obstet Gyncol. 2011;118:1454-8.

"Questions [on patient visit records] should be framed in ways that do not make assumptions about gender identity, sexual orientation, or behavior. It is more appropriate for clinicians to ask their patients which terms they prefer. Language should be inclusive, allowing the patient to decide when and what to disclose. The adoption and posting of a nondiscrimination policy can also signal health care providers and patients alike that all persons will be treated with dignity and respect. Assurance of confidentiality can allow for a more open discussion, and confidentiality must be ensured if a patient is being referred to a different health care provider. Training staff to increase their knowledge and sensitivity toward transgender patients will also help facilitate a positive experience for the patient."

b. American Psychiatric Association

Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder
Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. *Arch Sex Behav*. 2012; 41:759–96.

The American Psychiatric Association (APA) was unable to identify any Randomized Controlled Trials (RTCs) regarding mental health issues for transgender individuals.

"There are some level B studies examining satisfaction/regret following sex reassignment (longitudinal follow-up after an intervention, without a control group); however, many of these studies obtained data retrospectively and without a control group (APA level G). Overall, the evidence suggests that sex reassignment is associated with an improved sense of well-being in the majority of cases, and also indicates correlates of satisfaction and regret. No studies have directly compared various levels of mental health screening prior to hormonal and surgical treatments on outcome variables; however, existing studies suggest that comprehensive mental health screening may be successful in identifying those individuals most likely to experience regrets."

Relevant Descriptions of APA Evidence Coding System/Levels:

[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial."

[G] Other. Opinion-like essays, case reports, and other reports not categorized above."

c. Endocrine Society

Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. *J Clin Endocrinol Metab.* 2009;94:3132-54.

This guideline primarily addressed hormone management and surveillance for complications of that management. A small section addressed surgery and found the quality of evidence to be low.

"This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low."

d. World Professional Association for Transgender Health (WPATH)

Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (Version 7).
Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R. Wylie KR, Zucker K.
www.wpath.org/_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf
Int J Transgend. 2011;13:165–232.

The WPATH is "an international, multidisciplinary, professional association whose mission is to promote evidence-

based care, education, research, advocacy, public policy, and respect in transsexual and transgender health."

WPATH reported, "The standards of care are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b)."

The WPATH standards of care (SOC) "acknowledge the role of making informed choices and the value of harm-reduction approaches."

The SOC noted, "For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one's gender identity);
- Hormone therapy to feminize or masculinize the body;
- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience."

The SOC were carefully reviewed because they are frequently cited as the basis of management by clinicians, including some of the clinical groups with whom CMS spoke used it as a flexible guide. In the WPATH's SOC Appendix D titled "Evidence for Clinical Outcomes of Therapeutic Approaches," WPATH noted, "One of the real supports for any new therapy is an outcome analysis. Because of the controversial nature of sex reassignment surgery, this type of analysis has been very important. Almost all of the outcome studies in this area have been retrospective." They further reported, "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria."

e. American Psychological Association

Suggested citation until formally published in the *American Psychologist*: American Psychological Association. (2015): Guidelines for Psychological Practice with Transgender and Gender Nonconforming People
Adopted by the Council of Representatives, August 5 & 7, 2015. www.apa.org/practice/guidelines/transgender.pdf

"The purpose of the Guidelines for Psychological Practice with Transgender and Gender Nonconforming People (hereafter Guidelines) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and trans□affirmative psychological practice with TGNC people."

"These Guidelines refer to psychological practice (e.g., clinical work, consultation, education, research, training) rather than treatment."

5. Other Reviews

a. Institute of Medicine (IOM)

The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding.
Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. (Study Sponsor: The National Institutes of Health).
Issued March 31, 2011. http://www.nationalacademies.org/hmd/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and-Transgender-People.aspx

"To advance understanding of the health needs of all LGBT individuals, researchers need more data about the demographics of these populations, improved methods for collecting and analyzing data, and an increased participation of sexual and gender minorities in research. Building a more solid evidence base for LGBT health concerns will not only benefit LGBT individuals, but also add to the repository of health information we have that pertains to all people."

"Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

b. National Institutes of Health (NIH)

National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013.
http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf

In response to the IOM report, the NIH LBGT research Coordinating Committee noted that most of the health research for this set of populations is "focused in the areas of Behavioral and Social Sciences, HIV (human immunodeficiency virus)/AIDS, Mental Health, and Substance Abuse. Relatively little research has been done in several key health areas for LGBT populations including the impact of smoking on health, depression, suicide, cancer, aging, obesity, and alcoholism."

6. Pending Clinical Trials

ClinicalTrials.gov
There is one currently listed and recently active trial directed at assessment of the clinical outcomes pertaining to individuals who have had gender reassignment surgery. The study appears to be a continuation of work conducted by investigators cited in the internal technology assessment.

NCT01072825 (Ghent, Belgium sponsor) European Network for the Investigation of Gender Incongruence (ENIGI) is assessing the physical and psychological effects of the hormonal treatment of transgender subjects in two years prior to reassignment surgery and subsequent to surgery. This observational cohort study started in 2010 and is still in progress.

7. Consultation with Outside Experts

Consistent with the authority at 1862(l)(4) of the Act, CMS consulted with outside experts on the topic of treatment for gender dysphoria and gender reassignment surgery.

Given that the majority of the clinical research was conducted outside of the United States, and some studies took place in a or suggested continuity-of-care and coordination-of-care were beneficial to health outcomes, we conducted expert interviews with centers across the U.S. that provided some form of specialty-focused or coordinated care for transgender patients. These interviews informed our knowledge about the current healthcare options for transgender people, the qualifications of the professionals involved, and the uniqueness of treatment options. We are very grateful to the organizations that made time to discuss treatment for gender dysphoria with us.

From our discussions with the all of the experts we spoke with, we noted the following practices in some centers: (1) specialized training for all staff about transgender healthcare and transgender cultural issues; (2) use of an intake assessment by either a social worker or health care provider that addressed physical health, mental health, and other life factors such as housing, relationship, and employment status; (3) offering primary care services for transgender people in addition to services related to gender-affirming therapy/treatments; (4) navigators who connected patients with name-change information or other legal needs related to gender; (5) counseling for individuals, groups, and families; (6) an informed-consent model whereby individuals were often referred to as "clients" instead of "patients," and (7) an awareness of depression among transgender people (often measured with tools such as the Adult Outcomes Questionnaire and the Patient Health Questionnaire (8) and how, in some instances, with hormone treatment for gender dysphoria, the depression lessens.

8. Public Comments

Initial Comment Period: 12/03/2015 – 01/02/2016

During the initial comment period, we received 103 comments. Of those, 78% supported coverage of gender reassignment surgery, 15% opposed, and 7% were neutral. The majority of comments supporting coverage were from individuals and advocacy groups. All of the initial public comments are available at: https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=282&ExpandComments=n&bc=ACAAAAAAAgAAAA%3d%3d&

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under § 1862(l)(6) of the Act. In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage. Moreover, in most circumstances, the item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)). The Supreme Court has recognized that "[t]he Secretary's decision as to whether a particular medical service is 'reasonable and necessary' and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions." Heckler v. Ringer, 466 U.S. 602, 617 (1984). See also, 78 Fed. Reg. 48,164, 48,165 (August 7, 2013)

When making national coverage determinations, we consider whether the evidence is relevant to the Medicare beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully consider the demographic characteristics and comorbidities of study participants as well as the provider training and experience. This section of the proposed decision provides an analysis of the evidence, which included the published medical literature and guidelines pertaining to gender dysphoria, that we considered

during our review to answer the question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

A. Analysis

1. Study Demographics

These studies were conducted in a total of 13 countries. Most were conducted in Europe (a total of 24 in Europe: Belgium four, Germany four, Holland two, Norway one, Spain two, Sweden four, Switzerland three, the United Kingdom three [not including the Barrett, 1998 study and the duplicative Megeri, Khoosal, 2007 study], and Yugoslavia one). One was in Asia (Singapore); one in South America (Brazil). Seven were conducted in North America (U.S. six, Canada one). One of the North American studies was a U.S.-conducted internet survey with non-U.S. and U.S. participants with a sub-analysis of the U.S. patients (Newfield et al., 2006).

All of the studies, with the exception of a national-wide mortality study (Dhejne et al., 2011), the international internet survey (Newfield et al., 2006), and the internet/convention site survey (Ainsworth, Spiegel, 2010), were conducted with patient populations from single sites. Many of these clinical centers cited in these studies were specialized tertiary referral centers offering comprehensive, integrated (psychiatric-psychological, endocrine, and surgical) care and whose staff could have been involved in both the patient care and the study. Of the studies reviewed, the Lawrence, 2006 study was conducted by a physician psychologist who surveyed the patient population of a single U.S. surgeon. The Ainsworth, Spiegel, 2010 study was conducted by a U.S. otolaryngologist with extensive surgery training who assessed the impact of facial feminization on transgender patients. The Hess et al. 2014 study was undertaken at a German university urologic specialty clinic. The Wolfradt, Neumann, 2001 study was conducted in Germany by a university otorhinolaryngologist and psychologist on patients who had undergone vocal cord surgery after reassignment surgery. The Ruppin, Pfafflin 2015 study was undertaken by investigators who had seen the patients in a German forensic psychotherapy clinic.

2. Patient Population

Demographic assessments of the studies revealed that the mean ages of participants were in the 20s and 30s. (See Appendix C and Appendix D). Even when including standard deviation, most patients included in the study were under the age 60. Age of participants in the reviewed studies is important to assess generalizability to the Medicare population which is comprised predominantly of adults' age 65 years and older. While certain younger disabled adults are included in Medicare, generalizability of studies performed outside in the U.S. is likely reduced further since criteria to determine disability is unique to Medicare. When reporting ages of patients participating in studies, studies included mean age of population, but often failed to reveal standard deviation of the population. Most studies reported pre and post gender reassignment surgery ages, though some studies only reported post-surgery ages (Dehjne, 2011; Kuhn et al., 2009; Rakic et al., 1996; Ruppin, Pfafflin, 2015; Udeze et al., 2008; Megeri, Khoosal, 2007; Wolfradt, Neumann, 2001; Blanchard et al., 1985; Weyers et al., 2009; Wierckx et al., 2011; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Salvador et al., 2012; Tsoi, 1993).

There was extensive lack of study participation and loss to follow-up in the published studies. (See Appendix C and Appendix G). This suggests that the population that seeks evaluation/treatment for gender dysphoria and/or applies for reassignment surgery is not the same population that undergoes reassignment surgery without hesitation or regret. The notable numbers of incomplete questionnaires similarly raises questions. This selection bias limits generalizability of any results.

3. Study Design

As noted earlier, a number of research designs were found when exploring the question, "Does gender reassignment surgery improve health outcomes for Medicare beneficiaries with gender dysphoria?" (See Appendix C). The vast majority of studies found were observational in nature though there was a single randomized trial (Mate-Kole et al., 1990) (see Figure 1). Two of the studies were blinded. (Hess, 2014; Lawrence, 2006) A total of 29 studies were not blinded. The blinding status of the two internet surveys is unknown (Ainsworth, Spiegel, 2010; Newfield et al., 2006).

Observational studies can be prospective, retrospective, or have components of both. But each observational study design has limitations, and may not be able to show the true association between gender/reassignment surgery and improved health outcomes. Limitations of observational studies include that they frequently generate unreliable findings, and they also generate bias; because of confounding, causal inferences cannot reliably be drawn. Thus these types of studies are limited in terms of evidentiary weight. Only a true experimental study (e.g., randomized clinical trial) has the potential to demonstrate a causal relationship between two factors.

In general, one of the advantages of prospective studies is that they could potentially help determine factors associated with improved outcomes due to their longitudinal observation over time, and the collection of results at regular time intervals minimizes recall error. However, retrospective studies have problems including: some key statistics cannot be measured, significant biases including selection bias, recall bias, and information bias may limit a retrospective study's applicability. Another problem with retrospective studies is that the temporal relationship between variables is frequently difficult to assess. Finally, it is difficult to control exposure or outcome assessment in a retrospective study design.

Studies that use controls as part of its research design have higher evidentiary weight than studies that lack controls. That is because the use of controls can help to eliminate the possibility of confounding. But controls by themselves are no guarantee of complete validity. In terms of the use of controls in these studies that we evaluated some studies had no concurrent controls; some studies used control groups, but they were not concurrent; some studies used semi-matched controls; and in other studies patients served as their own controls.

Seventeen observational studies, of which 10 used longitudinal and 7 used cross-sectional study designs, had formal control groups. In this group of studies, the cross-sectional studies used various controls including healthy volunteers and patients with other disorders or treatments. In this same group of studies, the longitudinal studies used various controls including the patients as their own serial control, other treatment groups in addition to having patients serve as their own controls, and control cohorts derived from national databases. Among the longitudinal studies with used patients as their own controls, 4 used self-report test instruments that were validated in large populations. Of these 4, 1 had more than 100 subjects, self-reported and others, or other cohorts using either national data or national registries. Some observational studies included in this analysis had surgery-only populations and used no controls, or used indirect controls incorporating normative testing. The remainder of the observational studies had mixed populations that included surgical patients and patients using other treatments or patients treated with non-genital gender reassignment surgical procedures. The studies that included groups with mixed populations either had no controls, or used indirect controls (statistical methods included ANOVA, correlation, or regression).

Our review included 25 prospective studies. Of these prospective studies, two used a retrospective approach to acquire data for a single parameter (Eldh et al., 1997; Johansson et al., 2009); one prospective study used a retrospective approach to acquire data for several parameters (Ruppin, Pfafflin, 2015); and one study used a prospective approach beginning in 2003, but used a retrospective approach for data accumulated prior to that year (Leinung et al., 2013).

We found three retrospective studies (Asscheman et al., 2011; Dhejne et al., 2011; Landen et al., 1998). One study had at least a partially retrospective component, but with insufficient information to determine whether any of the data were obtained prospectively (Haraldsen, Dahl, 2000).

There were 11 longitudinal studies (Asscheman et al., 2011; Dhejne et al., 2011; Heylens et al., 2014; Kockott, Fahrner, 1987; Landen et al., 1998; Mate-Kole et al., 1979; Rakic et al., 1996; Ruppin, Pfafflin, 2015; Smith et al., 2005; Udeze et al,, 2008). Ten of the longitudinal studies occurred in the group of studies with a designated control group (all of the above with the exception of Asscheman et al., 2011). In seven of the 11 longitudinal studies, the patients served as their own control over time before and after surgery (Heylens et al., 2014; Kockott, Fahrner, 1987; Meyer, Reter, 1979; Rakic et al., 1996; Ruppin, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008).

There were 19 cross-sectional studies (Ainworth, 2010; Haraldsen, Dahl, 2000; Beatrice, 1985; Kraemer et al., 2008; Kuhn et al., 2009; Mate-Kole et al., 1988; Wolfradt, Neumann, 2001; Blanchard et al., 1985; Weyers et al., 2009; Wierckx et al., 2011; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Salvador et al., 2012; Tsoi, 1993; Gómez-Gil et al., 2012, Hepp et al., 2005; Motmans et al., 2012; Newfield et al., 2006; Gómez-Gil et al., 2013; Johansson et al., 2009; Leinung et al., 2013). Of this number, two were cross-sectional with the exception of data collection for aspects of a single parameter that had occurred in the past (Eldh et al., 1997; Johansson et al., 2009), and one study asked participants to recall the status of a parameter prior to treatment (Wierckx et al., 2011a).

Seventeen of the studies had explicit control groups. Of the studies with explicit control groups, two studies derived controls from national databases (Dhejne et al., 2011 and 2014; Landen et al., 1998); five studies used the patients themselves as longitudinal controls (Heylens 2014a; Rakic et al. 1996; Ruppin, Pfafflin, 2015; Smith et al., 2005a; Udeze et al., 2008; Megeri 2007); eight used various other controls (Ainsworth, Spiegel, 2010; Beatrice 1985; Haraldsen, Dahl, 2000; Kraemer et al., 2008; Kuhn et al., 2009; Mate-Kole et al., 1988 and 1990; Wolfradt, Neumann, 2001); and two studies used both treatment-type cohorts and patients themselves as controls (Kockott, Fahrner, 1987; Meyer, Reter 1979).

A number of studies consisted of surgical series, but in these studies there were no concurrent controls (Wierckx et al., 2011; Salvador et al., 2012; Blanchard et al., 1985; Tsoi, 1993; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Weyers, 2009a). In three surgical series normative data from psychometric instruments were used as the control (Blanchard et al., 1985a; Weyers 2009a; Wierckx et al., 2011b). In five surgical series, controls were lacking (except for the use of serial employment data in the Eldh et al. 1997 study) (Eldh et al., 1997; Hess 2014; Lawrence 2006; Salvador 2012; Tsoi, 1993).

Patients underwent a variety of surgical interventions in five studies. There were no controls. The role of surgical intervention was assessed indirectly *post hoc* by statistical techniques (analysis of variance and regression) (Gomez-Gil et al., 2012 and 2014; Hepp et al., 2005; Motmans et al., 2011; Newfield et al., 2006).

As mentioned in previous paragraphs, some prospective studies included in this analysis were cross-sectional in nature, and consisted of treated cohorts using a normative test, or a treatment cohort along with volunteer healthy cohorts. However, as we have noted, cross-sectional studies also have their limitations, including inability to determine temporal relationship between exposure and outcome (lacks time element). In other words, findings noted in a cross-sectional design cannot be inferred, because only current health and exposure to interventions are being studied. Also measurement error is an issue. Longitudinal studies with controls are most appropriate for determining this relationship between exposure and outcomes.

Observational studies have limitations. The lack of blinding has the potential to interfere with patient reported outcomes, which by their nature are subjective. Observational studies are prone to selection bias. Patients who seek treatment may not be the same as those who complete treatment-particularly if there are serial steps in the

treatment process. (See Appendix G) Cross-sectional studies are prone to confounding. The impact of a particular step in a multi-faceted treatment process cannot be ascertained. The lack of a control group does not permit attribution of any outcome change to a specific intervention. There were seven studies where the patients themselves serve as longitudinal controls. The lack of a control makes it difficult to assess the results because there is not another group to make comparisons.

4. Psychometric Measurement Tools

There is also myriad use of measurement tools to assess patients suffering with gender dysphoria. (See Appendix E for a list of Psychometric Measurement tools.)

Some of the domains addressed in psychometric measurement tools measure the degree of depression and anxiety, body imagery, quality of life, identity traits, general wellbeing, physical and psychological function, self-concept, and others. Some of these measurement tools have been validated for patients with this condition, while others have been validated for other medical conditions. Some of the measurement tools found in this assessment were self-developed and there is no mention of validity when trying to determine if the test reliably measures what it is intended to measure.

5. Study Endpoints

A wide variety of study endpoints were used. Endpoints were collected from a number of sources, including self-reporting, clinician assessment, and medical records as well national databases. Some of the endpoints included patient reported quality of life (QOL) as manifest by psychometric testing, sense of well-being, body imagery, anxiety and depression, sexual function and satisfaction, and social function. Objective endpoints included employment status, psychiatric function, and morbidity and mortality as well as adverse events.

Thirty of the studies employed 31 psychometric tools or investigator designed self-report surveys. (See Appendix E) Twenty investigators designed their own measurement tools or modified those of others.

External information on test validity, the size/composition of the reference population(s), diagnostic cut-points, and scoring was often not available because it was unpublished, proprietary, or in a non-English language. Six of the instruments, all non-specific, (the European QOL Survey, MMPI, SF-36, SCL-90, TSCS, and WHO-QOL-BREF), appear to have substantive normative data for comparative scoring (i.e., reference populations (≥1000) and obtained through representative sampling). Although these tools had been validated in a reference population, none had been validated in populations with gender dysphoria. Furthermore the investigators did not provide diagnostic cut-points and did not pre-specify the magnitude of test score change or test score difference considered to be biologically significant so the clinical importance could not be easily ascertained.

Only four investigator groups used only these psychometric tools validated in other large populations as their test instrument (Beatrice, 1985; Haraldsen, Dahl, 2000; Motmans et al., 2012; Newfield et al., 2006). Nine investigator groups used a mix of psychometric tools validated in large normative populations, less well validated tools, and/or self-designed tools (Ainsworth, Spiegel, 2010; Blanchard et al., 1985a; Gomez-Gil et al., 2014; Heylens 2014a; Ruppin, Pfafflin, 2015; Smith et al., 2005a (Udeze et al., 2008; Megeri 2007; Weyers 2009a; Wierckx et al., 2011b). Nine investigators used self-designed tools as their only test instrument (Eldh et al., 1997; Hess 2014; Johansson et al, 2009; Kockott, Fahrner, 1987; Lawrence, 2006; Meyer, Reter 1979; Rakic 1996; Salvador 2012; Tsoi 1993). A single investigator did not use any type of testing tool and provided only descriptive statistics (Leinung et al., 2013).

Three studies reported on complications linked or possibly linked to hormone treatment (Asscheman et al., 2011;

Dhejne et al., 2011; Leinung et al., 2013), six studies reported on complications from reassignment surgery (Eldh et al., 1997; Lawrence, 2006; Ruppin, Pfafflin, 2015; Smith et al., 2005; Weyers et al., 2009; Wierckx et al., 2011). One study reported on serious and formalized regret for undergoing reassignment surgery (Landen et al., 1998), and one study reported on a patient with suicidal ideation who requested phallus removal (Meyer, Reter, 1979). Others reported on less severe or less formalized levels of regret. Five studies reported on the treatment or diagnosis of psychiatric disease (Dhejne et al., 2011; Haraldsen, Dahl, 2000; Hepp et al., 2005; Landen et al., 1998; Leinung et al., 2013; Meyer, Reter, 1979; Ruppin, Pfafflin, 2015; Udeze et al., 2008). Two studies reported on the history of psychiatric disease in their patient populations (Matte-Kole, 1988; Matte Kole, 1990).

Four studies reported on suicide attempts (Dehjne et al., 2011; Eldh et al., 1997; Heylens et al., 2013; Kockott, Fahrner, 1987), two studies reported on the history of suicide attempts in their patient population (Matte-Kole, 1988; Matte Kole, 1990). Three studies reported on suicide, of which one of them occurred incidentally (Asscheman et al., 2011; Blanchard et al., 1985; Dhejne et al., 2011). Two studies also reported on mortality (Asscheman et al., 2011; Dhejne et al., 2011).

There was a great degree of inconsistency in endpoints. Also endpoints were collected from a number of sources, including self-reporting, clinician assessment, and medical records as well national databases. Endpoints lacked operational definitions thus making their applicability difficult. CMS is interested in knowing what patients diagnosed with gender dysphoria believe are important endpoints that should be studied.

Mortality and Regret as Endpoints

Certain kinds of objective outcomes can be assessed by other types of study designs-albeit somewhat less robust. These include mortality and regret (as manifest by request for surgical reversal) when the data are rigorously prospectively collected in a comprehensive registry for all patients who have met specified entry criteria and treatment criteria.

More specifically, Swedish investigators extracted data from registries at the National Board of Health and Welfare to which all patients seeking reassignment surgery or reversal of reassignment surgery must make formal application. In the initial 1998 study, of the 233 applicants for reassignment surgery between July 1972 and June 1992, 20 were denied surgery, and subsequently 13 (3.8%) surgical patients requested return to the natal sex (Landen et al., 1998). In the 2014 follow-up study, of the 767 applicants for reassignment surgery or a change in legal status after surgery between 1960-2010, 86 were denied, and subsequently 15 (2.2%) requested reversal to the natal gender (Dhejne et al., 2014). Although the data from the two studies are not directly comparable because of the much shorter follow-up period in the latter study and although the analyses also did not consider other possible expressions of regret including suicide, the studies suggest that the majority of highly vetted patients in a structured care system do not express regret as defined by a formal request for return to natal gender status (Dhejne et al., 2011). The study, however, cannot assess the impact of gender reassignment surgery per se because of the confounding introduced by the other interventions.

Swedish investigators also conducted the most comprehensive study with functional endpoints of the 33 studies reviewed. This study relied on compulsory national databases (Dhejne et al., 2011) tracked all patients who had undergone reassignment surgery (at a mean age 35.1 years) over a 30 year interval and compared them to 6480 matched controls from the general population. They identified both increased mortality and increased psychiatric hospitalization. The mortality was primarily due to completed suicides (19.1-fold greater), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. The divergence in mortality from the Swedish population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in control Swedes even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the sex of the control. For the same reasons as delineated above,

this study cannot assess the impact of gender reassignment surgery per se because of the confounding introduced by the other interventions. The finding of this study demonstrated that reassignment surgery does not return patients to a normal level of morbidity risk and that the morbidity risk is significant even in highly vetted patients in a structured care system.

B. Discussion

The question addressed in this NCD is whether there is sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria.

Gender dysphoria by the latest and prior nomenclature is a state in which there is incongruence between the gender assigned at birth and the gender(s) with which the person identifies. This incongruence may result in varying degrees of discontent and distress. Satisfaction and quality-of-life are well recognized as "latent variables" (hypothetical constructs) which cannot be measured directly (Borsboom et al., 2003; Newsom, 2015). As such, observable entities are used to infer or approximate satisfaction and/or quality-of-life. It may be challenging to identify parameters that truly reflect the nature and the magnitude of dysphoria in the individual. This challenge is followed by the need to know to what extent a specific test measures that which it purports to measure (test validity) and whether repeat testing will yield a comparable answer (test reliability).

The investigators of the clinical research reviewed in this NCD have attempted to measure dysphoria levels by objective data elements and by use of various psychometric and function scales/surveys. The objective data elements include a number of variables such as employment, morbidity, and formal requests for surgical reversal.

The psychometric tools used to assess outcomes have limitations. Many of the instruments that are most specific for the condition were designed by the investigators themselves or by other investigators in the field. In addition, the relevant diagnostic cut-points for scores and changes in scores that are clinically significant should be delineated to permit adequate interpretation of test results. As such, these studies were not definitive in nature.

Other factors might impact the utility of a given test. Patients undergo serial evaluations and a sequence of treatments (Bockting et al., 2011). These other interventions may reduce internal validity of the test. The affirmation and support obtained in psychotherapy-psychiatric care, the adjustment confidence gained in real life cross-gender behavior, and/or the physical and mental changes from hormone therapy may be (an) alternative cause(s) of the findings. Several studies suggest that there is a major therapeutic benefit from hormone therapy (Colizzi et al., 2013; Gómez-Gil et al., 2011; Gorin-Lazard et al., 2011, 2013; Heylens et al., 2014; Dubois, 2012). Another suggests that there is therapeutic benefit from time in the preferred gender role without other intervention (Greenberg, Laurence, 1981). As such, results from cross-sectional studies may be misleading. None of the studies used adequately matched controls over time. We believe longitudinal studies with serial assessment of the same patients would provide more robust answers. We note that even from the results from the four studies in which patients served as their own controls and which used an instrument known to be validated in large populations were negative (i.e., there was no improvement in psychometric or quality of life outcomes when patients were tested just prior to and at some point after the reassignment surgical intervention). (Heylens, 2014; Ruppin, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008). Further, rigorous studies with the use of appropriate comparison patients could better clarify the specific benefits and harms of each of the interventions.

CMS reviewed and considered potential objective measures of function including mortality, psychiatric treatment, and attempted suicide. None of the longitudinal studies in which patients served as their own control, however, comprehensively tracked changes in these events as objective measures of function before and after surgery. Events such as suicide and institutionalization were mentioned incidentally when describing patients excluded from a follow-up study or during the study (Heylens et al., 2014; Ruppin, Pfafflin, 2015). Other times investigators tracked these

functional outcomes (e.g., psychiatric out-patient treatment, psychiatric in-patient treatment, and substance abuse) for the most current prior year (Ruppin, Pfafflin, 2015).

The most comprehensive study with functional endpoints, the Swedish study that followed all patients who had undergone reassignment surgery (at mean age 35.1 years) over a 30 year interval and compared them to 6480 matched controls, identified increased mortality and increased psychiatric hospitalization (Dhejne et al., 2011). The mortality was primarily due to completed suicides (19.1-fold greater than in control Swedes), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. The divergence in mortality from the Swedish population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in controls even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the gender of the control. Unfortunately, the study was not constructed to assess the impact of gender reassignment *per se*. The finding of this study, again, demonstrated that reassignment surgery does not return patients to a normal level of morbidity risk and that the morbidity risk is significant, because of its clinical importance, its persistence over the interval of data collection and the increase in risk over time for the individual.

1. Patient Care

Additional questions regarding the care of patients with gender dysphoria remain. The specific type(s) of gender/sex reassignment surgery (genital, non-genital) that could improve health outcomes in adults remain(s) uncertain because most studies included patients who had undertaken one or more of a spectrum of surgical procedures or did not define the specific surgical procedures under study. Furthermore, most studies did not assess specific surgical procedures except for technical aspects. Surgical techniques have changed significantly over the last 60 years (Bjerrome Ahlin et al., 2014; Doornaert, 2011; Green, 1998; Pauly, 1968; Selvaggi et al., 2007; Selvaggi, Bellringer, 2011; Tugnet et al., 2007; Doornaert, 2011).

The WPATH care recommendations presented a general framework and guidance on the care of transgender individual. The standards of care are often cited by entities that perform gender reassignment surgery. WPATH noted: "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria." Appendix D in the WPATH Standards of Care acknowledged the historical problems with evidentiary standards, the preponderance of retrospective data, and the confounding impact of multiple interventions, specifically distinguishing the impact of hormone therapy from surgical intervention.

The surgical expertise and care setting(s) required to improve health outcomes in adults with gender dysphoria remain(s) uncertain. The selection of a particular surgeon could become an important variable if subjective outcomes depend on functional surgical results (Ross 1989). Many of these procedures involve complicated gynecologic, urologic surgical techniques accompanied by significant risk (Goddard et al., 2007a; Kuhn et al., 2011; Lawrence, 2003; Leclere et al., 2015; Rachlin, 1999; Ruppin, Pfafflin, 2015). Most of the studies for reassignment surgery have been conducted in northern Europe at select centers with integrated care (psychological, psychiatric, endocrinologic, and surgical) in which there is sequential evaluation of patients for progressively more invasive interventions.

Additionally, CMS met with several stakeholders and conducted several interviews with centers that focus on healthcare for transgender individuals in the U.S. Primary care was often the centers' main focus rather than gender reassignment surgery. Few of the U.S.-based reassignment surgeons we could identify work as part of an integrated practice, and few provide the most complex procedures.

2. Generalizability

With the variability in the study participants, providers and settings, the generalizability of the studies reviewed to

the Medicare population is unclear. Many of the studies are old since they were conducted more than 10 years ago. Many of the programs were single-site centers without replication elsewhere. Most of these studies were conducted outside of the U.S. with far different medical systems for treatment and follow-up. The study populations were young and without significant physical or psychiatric co-morbidity. As noted above psychiatric co-morbidity may portend poor outcomes (Asscheman et al., 2011; Landen et al., 1998).

For the above reasons, it is difficult to generalize these studies to the Medicare population.

3. Knowledge Gaps

This patient population faces complex and unique challenges. The medical science in this area is evolving. There are, however, many gaps in the evidentiary base. These gaps have been delineated because they represent areas in which patient care can be optimized and which are opportunities for much needed research.

The Institute of Medicine, the National Institutes of Health, and others have delineated many of the gaps in the data. (Boehmer, 2002; HHS-HP, 2011; IOM, 2011; Kreukels-ENIGI, 2012; Lancet, 2011; Murad et al., 2010; NIH-LGBT, 2013) The current or completed studies listed in ClinicalTrials.gov are not structured to assess these gaps.

The currently available evidence has limitations:

- There were design deficiencies. All but one of the studies were observational in nature. All but two were non-blinded. The accompanying loss to follow-up suggests that there is selection bias and that the population that seeks treatment for gender dysphoria is not the same population that undergoes reassignment surgery without hesitation or regret.
- The psychometric and psychosocial function endpoints are not well validated.
- There were limitations of the psychosocial endpoints and of the data collection of other hard functional outcomes. Evidence on mortality and especially suicide was stronger. The mortality and psychiatric hospitalization rates even after vetting in highly structured programs are of concern.
- There are insufficient data to select optimal candidates for surgery.
- The results were inconsistent, but negative in the best studies, i.e., those that reduced confounding by testing patients prior to and after surgery and which used psychometric tests with some established validation in other large populations. (Atkins et al., 2004; Balshem et al., 2011; Chan, Altman, 2005; Deeks et al., 2003; Guyatt et al., 2008a-c; 2011a-e; Kunz, Oxman,1998; Kunz et al., 2007 and 2011; Odgaard-Jensen et al., 2011).
- Data on reassignment surgery performed on geriatric patients or follow-up data in geriatric patients who had reassignment surgery in the distant past is anecdotal (Orel, 2014).

C. Health Disparities

Four studies included information on racial or ethnic background. The participants in the 3 U.S. based studies were predominantly Caucasian (Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006). All of the participants in the single Asian study were Chinese (Tsoi, 1993). Additional research is needed in this area.

D. Summary

Based on a thorough review of the clinical evidence available at this time, there is not enough evidence to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria. There were conflicting (inconsistent) study results – of the best designed studies, some reported benefits while others reported harms. The quality and strength of evidence were low due to the mostly observational study designs

with no comparison groups, potential confounding and small sample sizes. Many studies that reported positive outcomes were exploratory type studies (case-series and case-control) with no confirmatory follow-up. Due in part to the generally younger and healthier study participants, the generalizability of the studies to the Medicare population is also unclear. Additional research is needed. This proposed conclusion is consistent with the West Midlands Health Technology Assessment Collaboration (2009) that reported "[f]urther research is needed but must use more sophisticated designs with comparison groups." WPATH also noted the need for further research: "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria." Further, as mentioned earlier, patient preference is an important aspect of any treatment. With that in mind, CMS is interested in knowing from the patients with gender dysphoria what is important to them as a result of a successful gender reassignment surgery.

Knowledge on gender reassignment surgery for individuals with gender dysphoria is evolving. The specific role for various surgical procedures is less well understood than the role of hormonal intervention. Much of the available research has been conducted in highly vetted patients at select care programs integrating psychotherapy, endocrinology, and various surgical disciplines and operating under European medical management and regulatory structures. Standard psychometric tools need to be developed and tested in the patients with gender dysphoria to validly assess long term outcomes. As such, further evidence in this area would contribute to the question of whether gender reassignment surgery improves health outcomes in adults with gender dysphoria.

Because CMS is mindful of the unique and complex needs of this patient population and because CMS seeks sound data to guide proper care of the Medicare subset of this patient population, CMS strongly encourages robust clinical studies with adequate patient protections that will fill the evidence gaps delineated in this decision memorandum. As the Institute of Medicine (IOM, 2011) importantly noted: "Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

IX. Proposed Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

In the absence of a NCD, initial coverage determinations under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements will be made by the local Medicare Administrative Contractors (MACs) on an individual claim basis.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform the answer to the question posed in this proposed decision memorandum. Based on the gaps identified in the clinical evidence, these studies should focus on which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be developed that would support coverage with evidence development (CED), which would only cover gender reassignment surgery for beneficiaries who choose to participate in a clinical study.

X. Appendices

A. Appendix A

Diagnostic & Statistical Manual of Mental Disorders (DSM) Criteria for Disorders of Gender Identity since 1980

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III 1980 *Chapter: Psychosexual Disorders*	**Trans-sexualism** *302.5x [Gender Identity Disorder of Child-hood (302.6)]*	Required A (cross-gender identification) and B (aversion to one's natal gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	Sense of discomfort and inappropriateness about one's anatomic sex. Wish to be rid of one's own genitals and to live as a member of the other sex. The disturbance has been continuous (not limited to periods of stress) for at least 2 years.	Further characterization by sexual orientation Distinguished from Atypical Gender Identity Disorder 302.85
DSM III-Revised 1987 *TS classified as an Axis II dx (personality disorders and mental retardation) in a different chapter. GID included under Disorders Usually First Evident in Infancy, Childhood, Adolescence*	**Trans-sexualism** *(TS) (302.50) [GID of C]*	Required A and B criteria	Persistent discomfort and sense of inappropriateness about one's assigned sex. Persistent preoccupation for at least 2 years with getting rid of one's 1^{o} and 2^{o} sex characteristics and acquiring the sex characteristics of the other sex. Has reached puberty	Further characterization by sexual orientation Distinguished from Gender Identity Disorder of Adolescence or Adulthood, Non-trans-sexual Type • e.g., cross-dressing not for the purposes of sexual excitement Gender Identity Disorder Not Otherwise Specified 302.6 • e.g., intersex conditions Gender Identity Disorder Not Otherwise Specified

				302.85 • e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
	GID of adulthood, non-trans-sexual type, added			
DSM IV 1994 *Chapter: Sexual & Gender Identity Disorders*	**Gender Identity Disorder** in Adolescents and Adults (302.85) (Separate criteria & code for children, but same name)	Required A and B criteria Dx excluded by physical intersex condition	Cross-gender identification • e.g., Stated desire to be another sex • e.g., Desire to live or be treated as a member of the other sex • e.g., conviction that he/she has the typical feelings and reactions of the other sex • e.g., frequent passing as the other sex Persistent discomfort with his/her sex or sense of inappropriateness in the gender role of that sex. • e.g., belief the he/she was born the wrong sex • e.g., preoccupation with getting rid of 1^{o} and 2^{o} sex characteristics &/or acquiring sexual traits of the other sex • Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 • e.g., intersex conditions • e.g., stress related cross-dressing • e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM IV-Revised 2000 *Chapter: Sexual & Gender Identity Disorders*	**Gender Identity Disorder** (Term trans-sexual-ism eliminated)	Required A & B criteria Dx excluded by physical intersex condition	Cross-gender identification • e.g., stated desire to be the other sex • e.g., desire to live or be treated as the other sex • e.g., conviction that he/she has the typical feelings & reactions of the other sex • e.g., frequent passing as the other sex Persistent discomfort with his or her sex OR sense of inappropriateness in the gender role of that sex • e.g., belief the he/she was	Outcome may depend on time of onset Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 • e.g., intersex conditions • e.g., stress related cross-

			born the wrong sex • e.g., preoccupation with getting rid of 1^{O} and 2^{O} sex characteristics &/or acquiring sexual traits of the other sex Clinically significant distress or impairment in social, occupational, or other important areas of functioning	dressing • e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM V **2013** *Separate Chapter from Sexual Dysfunctions & Paraphilic Disorders*	**Gender Dysphoria** *(302.85)*	Gender nonconformity itself not considered to be a mental disorder The dysphoria associated with the gender incongruence is Eliminates A & B criteria Considers gender incongruence to be a spectrum Considers intersex/ "disorders of sex development" to be a subsidiary and not exclusionary to dx of GD	• Marked discordance between natal 1^{O} and 2^{O} sex characteristics* and experienced/expressed gender • Conviction that he/she has the typical feelings & reactions of the other sex (or some alternative gender) • Marked desire to be the other sex (or some alternative gender) • Marked desire to desire be treated as the other sex (or some alternative gender) • Marked desire to be rid of natal 1^{O} and 2^{O} sex characteristics** • Marked desire to acquire 1^{O} and 2^{O} sex characteristics of the other sex (or some alternative gender) Clinically significant distress or impairment in social, occupational, or other important areas of functioning * or in young adolescents, the anticipated 2^{O} sex characteristics ** or in young adolescents, prevent the development of the anticipated 2^{O} sex characteristics ≥ 6 month marked discordance between natal gender & experienced/expressed gender as demonstrated by ≥ 6 criteria: • Strong desire to be of the other gender or an insistence that one is of another gender. • Strong preference for cross-gender roles in make-believe play. • Strong preference for the toys, games, or activities of the other gender. • Strong preference for playmates of the other gender.	Includes diagnosis for post transition state to permit continued treatment access Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity syndromes

			• In boys, strong preference for cross-dressing; in girls, strong preference for wearing masculine clothing • In boys, rejection of masculine toys, games, activities, avoidance of rough and tumble play; in girls, rejection of feminine toys, games, and activities.	
	Unspecified Gender Dysphoria (302.6) (F64.9)		This category applies to presentations in which sx c/w gender dysphoria that cause clinically significant distress or impairment, but do not meet the full criteria for gender dysphoria & the reason for not meeting the criteria is not provided.	
	Specified Gender Dysphoria 302.6 (F64.8)		If the reason that the presentation does not meet the full criteria is provided then this dx should be used	

C/W=consistent with Dx=diagnosis GD=gender dysphoria Sx=symptoms TS=transsexual 1^{O}=primary 2^{O}=secondary

B. Appendix B

1. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or

co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one

of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix C

Patient Population: Enrolled & Treated with Sex Reassignment Surgery Loss of Patients & Missing Data

Panel A (Controlled Studies)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Dhejne 2011	Longitudinal Controlled	480 w GID who did not apply or were not approved for SRS were excluded	324	324 (100%)	-
Dhejne 2014 Landen	Longitudinal for test variable Controlled	767 applied for SRS 25 applications denied. 61 not granted full legal status 15 formal applications for surgical reversal	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper
Heylens	Longitudinal Controlled	90 applicants for SRS 33 excluded 11 later excluded had not yet received SRS by study close.	57 (→46)	46 (80.7%) Only those w SRS evaluated	Psycho-social survey missing data for 3 at baseline & 4 after SRS. SCL90 not completed by 1 at baseline, 10 after hormone tx, & 4 after SRS →missing data for another 1.1% to 11.1%.
Kockott	Longitudinal Controlled	80applicants for SRS 21 excluded	59	32 (54.2%) went to surgery	1 preoperative patient was later excluded b/c lived completely in aspired gender w/o SRS. Questions on financial sufficiency not answered by 1 surgical pt. Questions on sexual satisfaction & gender contentment not answered by 1 & 2 patients awaiting surgery respectively.
Mate-Kole 1990	Longitudinal Controlled	40 sequential patients of accepted patients. The number in the available patient pool	40	20 (50%) went to surgery	-

		was not specified.			
Meyer	Longitudinal Controlled	Recruitment pool: 100 52 excluded.	50	15 (30%) had undergone surgery 14 (28%) underwent surgery later	The assessments of all were complete
Rakic	Longitudinal Controlled	92 were evaluated 54 were excluded from surgery 2 post SRS were lost to follow-up 2 post SRS were excluded for being in the peri-operative period	32	32 (100%)	Questionnaire completed by all.
Ruppin	Longitudinal Controlled	The number in the available patient pool was not specified. 140 received recruitment letters. 69 were excluded	71	69 (97.2%)	The SCL-90, BSRI, FPI-R, & IPP tests were not completed by 9, 34, 13, &16 respectively. Questions about romantic relationships, sexual relationships, friendships, & family relationships were not answered by 1, 3, 2, & 23 respectively. Questions regarding gender security & regret & were not answered by 1& 2 respectively.
Smith	Longitudinal Controlled	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. 103 were excluded from additional tx	162	162 (100%)	36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete various post-SRS tests.
Udeze Megeri	Longitudinal Controlled	International patient w GD 546 & post SRS 318. 40 M to F subjects were prospectively selected.	40	40 (100%)	-
Ainsworth	Internet/convention Survey Cross-sectional Controlled	Number of incomplete questionnaires not reported	247	72 (29.1%) 75 (30.6%) facial 147 (59.5%) had received neither facial nor reassignment surgery	-

Beatrice	Cross-sectional Controlled	14 excluded for demographic matching reasons	40	10 (25%)	The assessments were completed by all
Haraldsen	Cross-sectional Controlled	Recruitment pool: 99	86	59 (68.6%)	-
Kraemer	Cross-sectional Controlled	The number in the available patient pool was not specified.	45	22 (48.9%)	-
Kuhn	Cross-sectional Controlled	The number in the available patient pool was not specified.	75	55 (73.3%)	-
Mate-Kole 1988	Cross-sectional Controlled	150 in 3 cohorts. Matched on select traits. The number in the available patient pool was not specified.	150	50 (66.7%)	-
Wolfradt	Cross-sectional Controlled	The number in the available patient pool was not specified.	90	30 (33.3%)	-

Panel B (Surgical Series: No Concurrent Controls)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Blanchard et al.	Cross-sectional Control: Normative test data	294 clinic patients w GD had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded	79	79(100%)	-
Weyers et al.	Cross-sectional Control: Normative test data	>300 M to F patients had undergone GRS 70 eligible patients recruited 20 excluded	50	50 (100%)	SF-26 not completed by 1
Wierckx et al.	Cross-sectional except for recall questions Control: Normative test data	79 F to M patients had undergone GRS & were recruited. 3 additional non-clinic patients were recruited by other patients. 32 excluded initially; 1 later.	49	49 (100%)	SF-36 test not completed by 2. Questions regarding sexual re-lationship, sex function, & surgical satisfaction were answered by as few as 27, 28, 32 respectively.
Eldh et al.	Cross-sectional except for 1 variable Control: Self for 1 variable-employ-ment	136 were identified. 46 excluded	90	90 (100%)	Questions regarding gender iden-tity, sex life, acceptance, & overall satisfaction were not answered by 13, 14, 14 & 16 respectively. Employment data missing for 11.

Hess et al.	Cross-sectional No control	254 consecutive eligible patients post GRS identified & sent surveys. 135 excluded.	119	119 (100%)	Questions regarding the esthetics, functional, and social outcomes of GRS were not answered by 16 to 28 patients.
Lawrence	Cross-sectional No control	727 eligible patients were recruited. 495 were excluded	232	232 (100%)	-
Salvador et al.	Cross-sectional No control	243 had enrolled in the clinic 82 completed GRS 69 eligible patients were identified. 17 excluded.	52	52 (100%)	-
Tsoi	Cross-sectional No control	The number in the available patient pool was not specified.	81	81 (100%)	-

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Gómez-Gil et al. 2012	Cross-sectional No direct control: Analysis of variance	200 consecutive patients were recruited. 13 declined participation or were excluded for incomplete questionnaires.	187	79 (42.2%)	See prior box.
Hepp et al.	Cross-sectional No direct control: Analysis of variance	The number in the available patient pool was not specified.	31	7 (22.6%)	HADS test not completed by 1
Motmans et al.	Cross-sectional No direct control: Analysis of variance & regression	255 with GD were identified. 77 were excluded.	148 (→140)	Not clearly stated. At least 103 underwent some form of GRS.	8 later excluded for incomplete SF-36 tests. 37 w recent GRS or hormone initiation were excluded from analysis of SF-36 results→103.
Newfield et al.	Internet survey Cross-sectional No direct control: Analysis of variance	Number of incomplete questionnaires not reported 446 respondents; 384 U.S respondents 62 non-U.S. respondents excluded from SF-36 test results 8 U.S. respondents excluded	376 (U.S.)	139 to 150 (37.0-39.9%) in U.S.	-
Gomez-Gil et al. 2014	Cross-sectional No direct control:	The number in the available patient pool	252(→193)	80 (41.4%) non-genital surgery	59 were excluded for incomplete

	Analysis w regression	was not specified. 277 were recruited. 25 excluded			questionnaires. See prior box.
Asscherman	Longitudinal No analysis by tx status	The number in the available patient pool was not specified.	1331	1177 (88.4%)	-
Johansson et al.	Cross-sectional except for 1 variable No analysis by tx status except for 1 question	60 eligible patients 18 excluded.	42	32 (76.2% of enrolled & 53.3% of eligible) (genital surgery)	-
Leinung et al.	Cross-sectional No analysis by tx status	242 total clinic patients	242	91 (37.6%)	Employment status data missing for 81 of all patients

*Data obtained via a survey on a website and distributed at a conference
B/C=because
BSRI=Bem Sex Role Inventory
F=Female
FP-R=Freiberg Personality Inventory
GD=Gender dysphoria
GID=Gender identity disorder
HADS=Hospital Anxiety & Depression Scale
IPP=Inventory of Interpersonal Problems
M=Male
NA=Not applicable
SCL-90=Symptom Checklist-90
SF-36=Short Form 36
GRS=Sex reassignment surgery
Tx=Treatment
W/o=without

Appendix D

Demographic Features of Study Populations

Panel A (Controlled Studies)

Author	**Age (years; mean, S.D., range)**	**Gender**	**Race**
Ainsworth	Only reassignment surgery:50 (no S.D.) Only facial surgery: 51 (no S.D.) Both types of surgery: 49 (no S.D.) Neither surgery: 46 (no S.D.)	247 M to F	-
Beatrice	Pre-SRS M to F: 32.5 (27-42), Post-SRS: 35.1 (30-43)	20 M to F plus 20 M controls	100% Caucasian
Dehjne 2011	Post-SRS: all 35.1±9.7 (20-69), F to M 33.3+8.7 (20–62), M to F 36.3+ 10.1(21–69)	133 (41.0%) F to M, 191 (59.0%) M to F; ratio 1:1.4	-
Dhejne 2014	F to M SRS cohort: median age 27 M to F SRS cohort: median age 32	767 applicants for legal/surgical reassignment	-

Landen	F to M applicants for reversal: median age 22 M to F applicants for reversal: median age 35	289 (37.7%) F to M, 478 (62.3%) M to F; ratio 1:1.6 681 post SRS & legal change 252 (37.0%) F to M, 429 (63.0%) M to F; ratio 1:1.7 15 applicants for reversal 5 (33.3%) F to M, 10 (66.7%) M to F; ratio 1:2	
Haraldsen	Pre-SRS & Post-SRS: F to M 34±9.5, F to M 33.3±10.0 Post-SRS cohort reportedly older. No direct data provided.	Pre & Post SRS 35 (40.7%) F to M, 51 (59.3%) M to F; ratio 1:1.5	-
Heylens	-	11 (19.3% of 57) F to M, 46 (80.7%); ratio 1:4.2 (80.7% underwent surgery)	-
Kockott	Pre-SRS (continued wish for surgery): 31.7±10.2 Post-SRS: 35.5±13.1	Pre-SRS (continued wish for surgery) 3 (25%) F to M, 9 (75%) M to F; ratio 1:3 Post SRS: 14 (43.8%) F to M, 18 (56.2%) M to F; ratio 1:1.3	-
Kraemer	Pre-SRS: 33.0±11.3, Post-SRS: 38.2±9.0	Pre-SRS 7 F to M (30.4%), 16 M to F (69.6%); ratio 1:2.3 Post-SRS 8 F to M (36.4%), 14 M to F (63.6%); ratio 1:1.8	-
Kuhn	All post SRS: median (range): 51 (39-62) (long-term follow-up)	3 (5.4%) F to M, 52 (94.5%) M to F; ratio 1:17.3.	-
Mate-Kole 1988	Initial evaluation: 34, Pre-SRS: 35, Post-SRS: 37	150 M to F	-
Mate-Kole 1990	Early & Usual wait SRS: 32.5 years (21-53)	40 M to F	-
Meyer	Pre-SRS: 26.7 Delayed, but completed SRS: 30.9 Post-SRS: 30.1	Pre-SRS: 5 (23.8%) F to M, 16 (76.2%) M to F; ratio 1:3.2 Delayed, but completed SRS: 1 (7.1%) F to M, 13 (92.9%) M to F; ratio 1:13 Post-SRS: 4 (26.7%) F to M, 11 (73.3%) M to F; ratio 1:2.8	86% Caucasian
Rakic	All: 26.8±6.9 (median 25.5, range 19-47), F to M: 27.8±5.2 (median 27, range 23-37), M to F: 26.4±7.8 (median 24, range 19-47).	10 (31.2%) F to M, 22 (68.8%) M to F; ratio 1:2.2	-
Ruppin	All: 47.0±10.42 (but 2 w/o SRS) (13.8±2.8 yrs post legal name change) (long-term follow-up) F to M: 41.2±5.78, M to F 52.9±10.82	36 (50.7%) F to M, 35 (49.3%) M to F; ratio 1:0.97	-
Smith	Time of surgical request for post-SRS: 30.9 (range 17.7-68.1) Time of follow-up for post-SRS: 35.2 (range 21.3-71.9)	Pre-SRS: 162: 58 (35.8%) F to M, 104 [64.2%] M to F; ratio 1:1.8 Post-SRS: 126: 49 (38.9%) F to M, 77 (61.1%) M to F; ratio 1:1.6	-
Udeze Megeri	M to F: 47.33±13.26 (range 25-80).	40 M to F	-

Wolfradt	Patients & controls: 43 (range 29-67).	30 M to F plus 30 F controls plus 30 M controls.	-

*Data obtained via a survey on a website and distributed at a conference SD=Standard deviation

Panel B (Surgical Series: No Concurrent Controls)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Blanchard et al.	F to M: 32.6, M to F w M partner preference: 33.2, F to M w F partner preference: 47.7 years	Post-GRS: 47 (45.6%) F to M, 56 (54.4%) M to F; ratio 1:1.19. In study: 38 (48.1%) F to M, 32 (40.5%) M to F w M partner preference, 9 (11.4%) M to F w F partner preference; ratio 1:0.8: 0.2	-
Weyers et al.	Post-GRS M to F: 43.1 ±10.4 (long-term follow-up)	50 M to F	-
Wierckx et al.	Time of GRS: 30±8.2 years (range 16 to 49) Time of follow-up: 37.1 ±8.2.4 years (range 22 to 54)	49 M to F	-
Eldh et al.	-	50 (55.6%) F to M, 40 (44.4%) M to F; ratio 1:0.8 There is 1 inconsistency in the text suggesting that these should be reversed.	-
Hess et al.	-	119 M to F	-
Lawrence	Time of GRS: 44±9 (range 18-70)	232 M to F	-
Salvador et al.	Time of follow-up for post-GRS: 36.28±8.94 (range 18-58) (Duration of follow-up: 3.8±1.7 [2-7])	52 M to F	-
Tsoi	Time of initial visit: All: 24.0±4.5, F to M: 25.4±4.4 (14-36), M to F: 22.9±4.6 (14-36). Time of GRS: All: 25.9±4.14, F to M: 27.4±4.0 (20-36), M to F: 24.7+4.3 (20-36).	36 (44.4%) F to M, 45 (55.6%) M to F; ratio 1:1.25	0% 100% Asian

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Gómez-Gil et al. 2012	W & W/O GRS: All: 29.87±9.15 (range 15-61), W/O hormone tx: 25.9±7.5, W current hormone tx: 33.6±9.1. (At hormone initiation: 24.6±8.1).	W/O hormone tx: 38 (56.7%) F to M, 29 (43.3%) M to F; ratio 1:0.8. W hormone tx: 36 (30.0%) F to M, 84 (70.0%) M to F; ratio 1:2.3. Post-GRS: 29 (36.7%) F to M, 50 (63.3%) M to F; ratio 1:1.7.	-
Hepp et al.	W & W/O GRS: 32.2±10.3	W & W/O GRS: 11 (35.5%) F to M; 20 (64.5%) M to F; ratio 1:1.8.	-
Motmans et	W & W/O GRS: All (n=140) : 39.9±10.2, F to	W & W/O GRS: N=140 63(45.0%) F	-

al.	M: 37.0±8.5, M to F: 42.3±10.4	to M, 77 (55.0%) M to F; ratio 1:1.2 N=103 49 (47.6%) F to M; 54 (52.4%) M toF; ratio 1:1.1	
Newfield et al.	W & W/O GRS: U.S.+ non-U.S. : 32.8±11.2, U.S. 32.6±10.8	W & W/O GRS: U.S.+ non-U.S.: F to M, 438, U.S.: F to M: 376	89% of 336 respondents Caucasian
Gomez-Gil, et al. 2014	W & W/O Non-genital GRS: 31.2±9.9 (range 16-67).	W & W/O Non-genital GRS: 74 (38.3%) F to M, 119 (61.7%) M to F; ratio1:1.6.	-
Asscherman	Time of hormone tx: F to M: 26.1±7.6 (16–56), M to F: 31.4±11.4 (16–76)	Met hormone tx requirements: 365 (27.4%) F to M, 966 (72.6%) M to F; ratio 1:2.6. Post-GRS: 343 (29.1%) F to M, 834 (70.9%) M to F; ratio 1:2.4.	-
Johanssen	Time of initial evaluation: F toM: 27.8 (18-46), M to F 37.3 (21-60). Time of GRS: F to M: 31.4 (22-49), M to F 38.2 (22-57). Time of follow-up for post-GRS: F to M: 38.9 (28-53), M to F 46.0 (25-69) (Long-term follow-up)	Approved for GRS: 21 (35%) F to M, 39 (65%) M to F; ratio 1:1.9) Post GRS: 14 (43.8%) F to M; 18 (56.2%) M to F; ratio 1:1.3)	-
Leinung et al.	Time of hormone initiation : F to M: 27.5, M to F 35.5	W & W/O GRS: 50 (20.7%) F to M, 192 M to F (79.3%); ratio 1:3.8. Post-GRS: 32 F to M (35.2%); 59 (64.8%) M to F; ratio 1:1.8.	-

Appendix E

Psychometric and Satisfaction Survey Instruments

Instrument Name and Developer	**Development and Validation Information**
APGAR Family Adaptability, Partner-ship Growth, Affection, and Resolve *Smilkstein*	Published in 1978 Initial data: 152 families in the U.S. A "friends" component was added in 1983. Utility has challenged by many including Gardner 2001
Beck Depression Inventory *Beck, Ward, Mendelson, Mock, & Erbaugh*	Published initially in 1961 with subsequent revisions It was initially evaluated in psychiatric patients in the U.S.A. Salkind (1969) evaluated its use in 80 general outpatients in the UK. Itis copyrighted and requires a fee for use
Bem Sex Role Inventory *Bem*	Published 1974 Initial data: 100 Stanford Undergraduates 1973 update: male 444; female 279 1978 update: 470; female 340
Body Image Questionnaire *Clement & Lowe*	Validity study published 1996 (German) Population: 405 psychosomatic patients, 141 medical students, 208 sports students
Body Image Scale	1975

Lindgren & Pauly (Kuiper, Dutch adaptation 1991)	Initial data: 16 male and 16 female transsexual patients in Oregon
Crown Crisp Experiential Index (formerly Middlesex Hospital Questionnaire) *Crown & Crisp*	Developed circa 1966 Manual published 1970 Initial data: 52 nursing students while in class in the UK
(2nd) European Quality of Life Survey *Anderson, Mikuliç, Vermeylen, Lyly-Yrjanainen, & Zigante,*	Published in 2007 The pilot survey was tested in the UK and Holland with 200 interviews. The survey was revised especially for non-response questions. Another version was tested in 25 persons of each of the 31 countries to be surveyed. Sampling methods were devised. 35,634 Europeans were ultimately surveyed. Additional updates
Female Sexual Function Index *Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, Ferguson, D'Agostino Wiegel, Meston, & Rosen*	Published in 2000 Initial data: 131 normal controls & 128 age-matched subjects with female sexual arousal disorder from 5 U.S. research centers. Updated 2005: the addition of those with hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia/vaginismus, & multiple sexual dysfunctions (n=568), plus more controls (n=261).
Fragebogen zur Beurteilung des eigenen Korpers *Strauss*	Published 1996 (German)
Freiberg Personality Inventory *Fahrenberg, Hampel, & Selg*	7th edition published 2001, 8th edition in 2009 (Not in PubMed) German equivalent of MMPI
"gender identity disorder in childhood" *Smith, van Goozen, Kuiper, & Cohen-Kettenis*	11 items derived from the Biographical Questionnaire for Trans-sexuals (Verschoor Poortinga 1988) (Modified by authors of the Smith study)
Gender Identity Trait Scale *Altstotter-Gleich*	Published 1989 (German)
General Health Questionnaire *Goldberg & Blackwell (initial study)* *Goldberg & Williams (manual)*	Initial publication 1970 Manual published ?1978, 1988 (Not in PubMed) Initial data: 553 consecutive adult patients in a single UK primary care practice were assessed. Sample of 200 underwent standardized psychiatric interview. Developed to screen for hidden psychological morbidity. Proprietary test. Now 4 versions.
Hospital Anxiety & Depression Scale *Zigmond & Snaith*	Published in 1983 Initial data: Patients between 16 & 65 in outpatient clinics in the UK >100 patients; 2 refusals. 1st 50 compared to 2nd 50.

Inventory of Interpersonal Problems *Horowitz*	Published 1988 Initial data: 103 patients about to undergo psychotherapy; some patients post psycho-therapy (Kaiser Permanente-San Francisco) Proprietary test
King's Health Questionnaire *Kelleher, Cardozo, Khullar, & Salvatore*	1997 Initial data: 293 consecutive women referred for urinary incontinence evaluation in London Comparison to SF-36
Minnesota Multi-phasic Personality Inventory *Hathaway & McKinley* *Butcher, Dahlstrom, Graham, & Tellegen*	Published in 1941 Updated in 1989 with new, larger, more diverse sample. MMPI-2: 1,138 men & 462 women from diverse communities & several geographic regions in the U.S.A. The test is copyrighted.
Modified Androphia-Gynephilia Index	Neither the underlying version or the Blanchard modified version could be located in PubMed (Designed by the author of the Blanchard et al. study)
"post-operative functioning 13 items" *Doorn, Kuiper, Verschoor, Cohen-Kettenis*	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
"post-operative functioning 21 items" *Doorn, Kuiper, Verschoor, Cohen-Kettenis*	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
Scale for Depersonalization Experiences *Wolfradt*	Unpublished manuscript 1998 (University of Halle) (Designed by 1 of the authors of the Wolfradt study)
"sex trait function" *Cohen-Kettenis & van Goozen*	Published 1997 Assessed in 22 adolescents (Designed by 1 of the authors of the Smith Study)
Self-Esteem Scale *Rosenberg*	Published 1965 (Not in PubMed) Initial data: 5,024 high-school juniors & seniors from 10 randomly selected New York schools
Short-Form 36 *RAND* *Ware & Sherbourne1992* *McHorney, Ware, & Raczek 1993*	Originally derived from the Rand Medical Outcomes Study (n=2471 in version 1; 6742 in version 2 1989). The earliest test version is free. Alternative scoring has been developed. There is a commercial version with a manual.
Social Anxiety & Distress Scale *Watson & Friend*	Initial publication in1969 Requires permission for use
Social Support Scale *Van Tilburg 1988*	Published 1988 (Dutch) (Not in PubMed)
Spielberger State & Trait Anxiety Questionnaire *Spielberger, Gorsuch, Lushene, Vagg, & Jacobs*	Current format published in 1983 Proprietary test

Symptom Checklist-90 *Derogatis, Lipman, Covi Derogatis & Cleary*	Published in 1973 & 1977 Reportedly with normative data for psychiatric patients (in- & out-patient) & normal subjects in the U.S. Has undergone a revision Requires qualification for use
Tennessee Self-Concept Scale *Fitts & Warren*	In use prior to 1988 publication. Initial data: 131 psychiatric day care patients. Updated manual published 1996. Update population >3000 with age stratification. No other innformation available. Requires qualification for use
Utrecht Gender Dysphoria Scale *Cohen-Kettenis & van Goozen*	Published in 1997 Initial population: 22 transgender adolescents who underwent reassignment surgery. (Designed by 1 of the authors of the Smith study)
WHO-Quality of Life (abbreviated version) *Harper for WHO group*	Field trial version released 1996 Tested in multiple countries. The Seattle site consisted of 192 of the 8294 subjects tested). Population not otherwise described. The minimal clinically important difference has not been determined. Permission required

Althof et al., 1983; Greenberg, Frank, 1965; Gurtman, 1996; Lang, Vernon, 1977; Paap et al., 2012; Salkind et al., 1969; Vacchiano, Strauss, 1968.

Appendix F

Endpoint Data Types and Sources

Panel A (Controlled Studies)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substan-tive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne 2011	Yes	-	-	-	-	Criminality, Mortality (Suicide, Cardiovascular Disease [possible adverse events from Hormone Tx], Cancer), Psych hx & hospitalization, Suicide attempts
Dhejne Landen	Yes	-	-	-	Includes demographics*	Criminality, Education, Employment, Formal application for reversal of status, Psych dx & tx, Substance abuse** More elements in earlier

						paper
Beatrice	-	MMPI form R, TSCS	-	-	Demographic	Education, Income, Relationships
Haraldsen	-	SCL-90/90R	-	-	Demographic	DSM Axis 1, II, V (GAF), Substance abuse
Heylens	-	SCL-90	-	Yes-2	Demographic	Employment, Relationships, Substance abuse, Suicide attempts
Ainsworth	-	Likely SF-36v2*	-	Yes-1	Demographic	-
Ruppin	-	SCL-90R	BSRI, FPI-R, IIP	Yes-2	Demographic	Adverse events from surgery, Employment, Psych tx, Relationships, Substance abuse
Smith	-	MMPI-short, SCL-90?R	BIS, UGDS, ? Cohen-Kettenis', Doorn's x2, (Gid-c, SSS)	Yes-1 or 2	Demographic	Adverse events from surgery, Employment, Relationships
Udeze Megeri	-	SCL-90R	BDI, GHQ, HADS,STAI-X1, STAI-X2	-	-	Psych eval & ICD-10 dx
Kuhn	-	-	KHQ	Yes-1	Demographic	Relationships
Mate-Kole 1990	-	-	BSRI, CCEI	Yes-1	Demographic	Employment (relative change), Psych hx, Suicide hx
Wolfradt	-	-	BIQ, GITS, SDE, SES	Yes-1	-	-
Kraemer	-	-	FBeK	-	Demographic	-
Mate-Kole 1988	-	-	BSRI, CCEI	-	Demographic	Employment, Psych hx, Suicide hx,
Kockott	-	-	-	Yes-1	Demographic	Employment, Income, Relationships, Suicide attempts
Meyer	-	-	-	Yes-1	Demographic	Education, Employment, Income, Psych tx, Phallus removal request
Rakic	-	-	-	Yes-1	Demographic	Employment, Relationships

Panel B (Surgical Series: No Concurrent Controls)

Author	**National Data**	**Instrument w Substantive Normative Data**	**Instrument w/o Substantive &/or Accessible Normative Data**	**Investigator-designed**	**Other**	**Other**
Weyers	-	SF-36	FSFI	Yes-2	Demographic	Hormone levels,

						Adverse events from surgery, Relationships
Blanchard	-	SCL-90R	(AG)	Yes-1	Demographic	Education, Employment, Income, Relationships, Suicide (Incidental finding)
Wierckx	-	SF-36	-	Yes-3	Demographic	Hormone levels, Adverse events from surgery, Relationships
Eldh	-	-	-	Yes-1	-	Adverse events from surgery, Employment, Relationships, Suicide attempts
Hess	-	-	-	Yes-1	-	-
Lawrence	-	-	-	Yes-4	Demographic	Adverse events from surgery
Salvador	-	-	-	Yes-1	Demographic	Relationships
Tsoi	-	-	-	Yes-1	Demographic	Education, Employment, Relationships (relative change)

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	**National Data**	**Instrument w Substantive Normative Data**	**Instrument w/o Sub-stantive &/or Accessible Normative Data**	**Investigator-designed**	**Other**	**Other**
Asscheman et al.	Yes	-	-	-	Demographic	Mortality (HIV, Possible adverse events from Hormone Tx, Substance abuse, Suicide)
Motmans et al.	-	SF36 EQOLS (2nd)	-	-	Demographic	Education, Employment, Income, Relationships

Newfield et al.	-	SF-36v2	-	-	Demographic	Income
Gómez-Gil et al. 2014	-	WHOQOL-BREF	APGAR	Yes-1	Demographic	Education, Employment, Relationships
Gómez-Gil et al. 2012	-	-	HADS, SADS	-	Demographic	Education, Employment, Living arrangements
Hepp et al.	-	-	HADS	-	Demographic	DSM Axis 1& II Psych dx
Johansson et al.	-	-	-	Yes-1	Demographic	Axis V change (Pt & Clinician) Employment (relative change) Relationship (relative change)
Leinung et al.	-	-	-	-	Demographic	Employment, Disability, DVT, HIV status, Psych dx

*Listed as San Francisco-36 in manuscript

** From medical charts & verdicts ?=Possibly self-designed

AG=Androphilia-Gynephilia Index (investigator designed 1985) (used more for classification)

APGAR=Family Adaptability, Partnership growth, Affection, and Resolve

BDI=Beck Depression Inventory

BIQ=Body Image Questionnaire

BIS=Body Image Scale

BSRI=Bem Sex Role Inventory

CCEI=Crown Crisp Experiential Index

Cohen-Kettenis'= Sex trait function (An author helped design)

Dorn's x2= Post-operative functioning 13 items (An author helped design)

Post-operative functioning 21 items (An author helped design)

EQOLS (2nd)=2nd European Quality of Life Survey

FBeK=Fragebogen zur Beurteilung des eigenen Korpers

FPI-R=A version of the Freiberg Personality Inventory

FSFI+Female Sexual Function Index

GHQ=General Health Questionnaire

Gid-c=Gender identity disorder in childhood (used more for predictors) (An author helped design)

GITS=Gender Identity Trait Scale

HADS=Hospital Anxiety Depression Scale

IIP=Inventory of Interpersonal Problems

KHQ=King's Health Questionnaire

MMPI=Minnesota Multi-phasic Personality Inventory

SADS=Social Anxiety & Distress Scale

SCL-90 (±R)=A version of the Symptom Checklist 90

SDE=Scale for Depersonalized Experiences (An author designed)

SES=Self-Esteem Scale

SF-36 (v2)=Short Form-36(version2)

SSS=Social Support Scale (used more for predictors)

STAI-X1, STAI-X2=Spielberger State and Trait Anxiety Questionnaire
TSCS=Tennessee Self-Concept Scale
UGDS=Utrecht Gender Dysphoria Scale (An author helped design)
WHOQOL-BREF=World Health Organization-Quality of Life (abbreviated version)

Appendix G.

Longitudinal Studies Which Used Patients as Their Own Controls and Which Used Psychometric Tests with Extensive Normative Data or Longitudinal Studies Which Used National Data Sets

Author		Test	Patient and Data Loss	Results
		Psychometric Test		
Heylens et al. Belgium 2014		SCL-90R	90 applicants for SRS were recruited. • 8 (8.9%) declined participation. • 12 (13.3%) excluded b/c GID-NOS dx. • 12 (13.3%) did not complete the treatment sequence b/c of psychiatric/physical co-morbidity, personal decision for no tx, or personal decision for only hormone tx. • 1 (1.1%) committed suicide during follow-up. 57 (63.3% of recruited) entered the study. • 1 (12.2% of initial recruits) had not yet received SRS by study close. →**46 (51.1% of recruited) underwent serial evaluation** • The test was not completed by 1 at t=0, 10 at t=1 (after hormone tx), & 4 at t=2 (after SRS) →**missing data for another 1.1% to 11.1%.**	At t=0, the mean global "psychoneuroticism" SCL-90R score, along with scores of 7 of 8 subscales, were statistically more pathologic than the general population. After hormone tx, the mean score for global "psychoneuroticism" normalized & remained normal after reassignment surgery.
Ruppin,Pfafflin, Germany 2015		SCL-90R	The number in the available patient pool was not specified. 140 received recruitment letters. • 2 (1.4% of those with	At t=0, the "global severity index "SCL-90R score was 0.53±0.49. At post-SRS follow-up the score had decreased to 0.28±0.36.

			recruitment letters) had died. • 1 (0.7%) was institutionalized. • 5 (3.6%) were ill. • 8 (5.7%) did not have time. • 8 (5.7%) stated that GD was no longer an issue. • 8 (5.7%) provided no reason. • 28 (20.0%) declined further contact. • 9 (6.4%) were lost to follow-up. →**71 (50.7%) agreed to participate.** **• 2 (1.4%) had not undergone SRS** • The test was not completed by 9. →**missing data for another 6.4%.**	The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 0-4. In the same way, all of the subscale scores were statistically different, but the effect size was reported as large only for "interpersonal sensitivity": 0.70±0.67 at t=0 and 0.26±0.34 post-SRS.
Smith et al. Holland 2005		MMPI SCL-90	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. • 103 (31.7%) were not eligible to start hormone tx & real-life experience. • 34 (10.7%) discontinued hormone tx 162 (an unknown percentage of the initial recruitment) provided pre-SRS test data. **• 36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete post-SRS testing.**	Most of the MMPI scales were already in the normal range at the time of initial testing. At t=0, the global "psychoneuroticism" SCL-90 score, which included the drop-outs, was 143.0±40.7. At post SRS-follow-up, the score had decreased to 120.3±31.4. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 90 to 450, with higher scores consistent with more psychological instability.
Udeze, et al. 2008 Megeri, Khoosal 2007 UK		SCL-90R	The number in the available patient pool was not specified. 40 subjects were prospectively selected. • Post-operative testing was conducted within 6	At t=0, the mean raw global score was 48.33. At post-SRS follow-up, the mean score was 49.15. There were no statistically

			months to minimize previously determined loss rates.	significant changes in the global score or for any of the subscales.
	National Databases			
Dehjne Sweden 2011		Swedish National Records	804 with GID in Sweden 1973 to 2003 were identified. • 480 (59.7%) did not apply or were not approved for SRS 324 (40.3%) underwent SRS. • All were followed. 3240 controls of the natal sex and 3240 controls of the reassigned gender were randomly selected from national records	All cause mortality was higher (n=27[8%]) than in controls (H.R 2.8 [1.8-4.3]) even after adjustment for covariants. Divergence in survival curves was observed after 10 years. The major contributor was completed suicide (n=10 [3%]; adjusted H.R. 19.1 [5.8-62.9]). Suicide attempts were more common (n= 29 [9%]) than in controls (adjusted H.R. 4.9 [2.9–8.5]). Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common n= 64 [20%] than in controls (H.R. 2.8 [2.0–3.9]) even after adjusting for prior psychiatric morbidity.
Dhejne et al. 2014 Landen et al. 1998 Sweden		Swedish National Registry	767 applied for SRS/legal status (1960-2010) • 25 (3.3%) applications denied. • 61 (8.0%) not granted full legal status 681 (88.7%) underwent SRS. • All were followed.	15 formal applications for reversal to natal/original gender (2.2% of the SRS population) were identified thus far (preliminary number). (Does not reflect other manifestations of regret such as suicide.)

GID-NOS=Gender Identity Disorder-Not Otherwise Specified HR=Hazard Ratio SRS=Sex reassignment surgery Tx=Treatment

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