Technical Brief Research Review Disposition of Comments Report

Research Review Title: *Maternal-Fetal Surgical Procedures*

Draft review available for public comment from June 2009 to July 2009.

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Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Introduction	“operations” is better than “surgeries”	Thank you for your suggestion. We agree that the word “surgeries” can be imprecise. Therefore, we have changed the term to either operations or surgical procedures throughout the document.
Peer Reviewer #13	Introduction	The authors have stated that "There are currently several trials sponsored by the NIH underwasy to evaluate some of the most common fetal surgeries." At the time of this manuscript this reviewer is only aware of one trial, The MOMs RCT for Open Spina bifida, that is funded by the NIH which is addressing risk/benefits of fetal surgery vs. traditional postnatal care. What other trials specifcially on fetal surgery are the authors referencing?	We have modified the wording in the text and updated our table.
Peer Reviewer #7	Introduction	Add reproductive future as one of the risks of maternal-fetal surgery	We have made this change in the text
Peer Reviewer #3	Introduction	The report cites the first open surgery for obstructive uropathy in 1981. Since open fetal surgery has essentially been replaced by Endoscopic Fetal Surgery, a reference to this other approach would be justified.	We have modified this statement to reflect endoscopic surgery as well.
Peer Reviewer #3	Introduction	The IFMSS is a think-tank for fetal surgery, with no authority to issue guidelines on the practice of fetal therapy. In fact, the IFMSS has requested that abstracts presented by investigators at its meetings not constitute a prior publication for other meetings, such as SMFM. Therefore, no single investigator can claim ownership of the opinion of this multidisciplinary group in any given subject or principle. A blatant incongruence with the principles quoted is the fact that an animal model does not exist for twin-twin transfusion syndrome, the most common condition amenable for fetal therapy today.	Thank you for this excellent point. We have replaced the word "guidelines" with "principles" which we believe is a more accurate term.

Peer Reviewer #7	Introduction	".behind them and of or are being…" too many words ('and of')	Corrected.
Peer Reviewer #7	Introduction	"Study design of size of country of setting" – nonsensical sentence	Corrected.
Peer Reviewer #8	Introduction	No comment	
Peer Reviewer #7	Methods	"…Consultant, and of or…" – again, too many words: 'and of'	Corrected
Peer Reviewer #7	Methods	"Adverse events of harms of safety issues" - sentence	Corrected
Peer Reviewer #13	Methods	Question regarding stats, N/A	Nature of the comment is unclear. No changes made.
Public Reviewer #3	Methods	Please look more fully for out of US information (ongoing trials/studies; evaluations done or underway by any other national bodies in other countries; guidelines from other countries; statements from professional societies/colleges in other countries.	Thank you - we have gathered as much information as we were able to find through the internet and requests to key informants. In a new and ever-changing field, it is certainly challenging to capture all information.
Peer Reviewer #3	Results	Page 10 does not mention the USFetus, despite the fact that this group performs the highest volume of fetal surgeries in the United States today. This contrasts with the inclusion of "member of NAFNET" as a column in Table 3. This appears as obvious advertisement for this group.	Thank you for pointing this out. We have added USFetus to this section.
Peer Reviewer #3	Results	The statement "open surgery in general has typically been in the realm of pediatric surgeons, who are surgeons first and foremost in their training and expertise" is offensive. Do the authors suggest that other fetal therapists are less qualified, or second-class	This section presents multiple perspectives contributing differing observations. Since none are based on empiric evidence, we have deleted the section from the report.

		citizens? The subsequent statement "Conversely, extensive training and experience in using ultrasound-guided techniques…invasive approaches" falls short of establishing a balanced view.	
Peer Reviewer #3	Results	The statement on page 13 that "Fetal Surgery in Europe is, in fact, primarily in the purview of obstetricians, whereas its development has been led more in the United States by pediatric surgeons,…"is also inaccurate. Open fetal surgery has been led both in Europe as well as in the US by pediatric surgeons. Endoscopic Fetal Surgery has been led by Maternal-Fetal Medicine Specialists.	This section presents multiple perspectives contributing differing observations. Since none are based on empiric evidence, we have deleted the section from the report.
Peer Reviewer #3	Results	Similarly, the statement "In the United States, pediatric surgeons are trained first as surgeons, with OBGYNs receiving less surgical training; whereas in Europe, obstetrical training is more focused on surgery…" is inaccurate in two accounts: first, it suggests that OBGYNs have less surgical training for fetal surgery than pediatric surgeons. Second, it suggests that the surgical training in OBGYN in Europe is more surgical than in the United States.	This section presents multiple perspectives contributing differing observations. Since none are based on empiric evidence, we have deleted the section from the report.
Peer Reviewer #3	Results	Page 13 further explains how the pediatric surgeon driven model is exemplified at UCSF and other centers (CHOP). The report does not exemplify the Maternal-Fetal Medicine model in the United States.	This section of the report has been deleted.
Peer Reviewer #3	Results	Page 15 states that "a key informant involved in this approach…". The names of other physicians or institutions are used in the section. Not mentioning the name of the "key informant" or his/her institution is an obvious bias.	We have deleted this sentence and added additional references discussing the potential of telemedicine approaches.
Peer Reviewer #3	Results	Page 31, "The Harrison group at UCSF dominates this literature" is an unnecessary and outdated accolade. The current literature is focused on a minimally-invasive approach to palliate the condition (CDH), after	During the full timeframe reviewed the Harrison group is responsible for 7 of the 18 papers that met criteria for review. This statement is not intended

		20 years of failed attempts by the open fetal surgery approach. In fact, the poorly conducted randomized clinical trial in the United States (100% prematurity, 100% premature rupture of membranes, use of multiple ports including 10mm trocars in the treatment group), which did not include reporting on neurological morbidity (50% in each arm, of less than 50% of those studied) threatened to halt all efforts in finding a viable antenatal solution for this problem. The current literature on CDH is not US dominated.	as an acccolade; rather it is a statement based on paper counts and is introduced here to convey that the literature is biased to the degree that a single group is numerically over-represented in understanding these outcomes. Nonetheless, we have modified the language to "is responsible for."
Peer Reviewer #3	Results	The technique for fetal tracheal occlusion (page 35) was first published by me (Quintero et al. Minimally-invasive intraluminal tracheal occlusion in a human fetus with left congenital diaphragmatic hernia at 27 weeks' gestation via direct fetal laryngoscopy. Prenatal Neonat Med 2000; 5:134-40), and not from "FETENDO" . In fact, FETENDO was the failed endoscopic surgical approach used in the RCT conducted in the United States, with the list of complications mentioned above. The Europeans did not "take advantage of the earlier U.S. experience", but rather avoided making all of the mistakes of the US trial by adhering to a minimally-invasive approach and using the direct fetal laryngoscopy approach developed by me and shared with them.	Thank you. We have changed the text per your suggestion. Unfortunately, we cannot include your paper in this review as single case reports were not an included study design for inclusion.
Peer Reviewer #3	Results	Page 40, on MMC, states that "…several experts in the literature (cited reference 120, Chervenak et al) have suggested that this trial appropriately put a stop to a proliferation of centers doing in utero MMC…". Perhaps the Editors are not aware that Dr. Harrison performed a case of MMC via open fetal surgery in Buenos Aires, Argentina during the time the MOMs trial was being conducted. This surgery, which appeared in the front page of the local newspapers, is at odds with the scientific commitment that this investigator has shown over the years.	Noted; neither the review process nor the document sought to track the activities of indiviudal surgeons.

Peer Reviewer #3	Results	The section on CCAM, including Table 17, did not include our publication of percutaneous ultrasound-guided fetal sclerosis of these lesions (Bermudez et al. Percutaneous Fetal Sclerotherapy for Congenital Cystic Adenomatoid Malformation of the Lung; Fetal Diagn Ther 2008; 24:237-240). This minimally-invasive approach has essentially removed the indication for open fetal surgery for CCAM associated with hydrops.	We have added a reference to this paper in a section of the review noting novel findings in CCAM therapy.
Peer Reviewer #3	Results	On page 62, on TTTS, the Editors mention "septostomy" as a treatment alternative. This procedure is probably the most deleterious, ill-founded and scientifically proven not-to- be-of-benefit fetal intervention ever.	We have added a statement to indicate that septostomy is not a standard treatment.
Peer Reviewer #3	Results	Page 62 also contains an error in the definition of selective laser therapy. The statement should say: "In non-selective ablation, all vessels crossing the dividing membrane are ablated, whereas selective ablation is limited to vessels shown to be communicating between the two fetuses."	Corrected.
Peer Reviewer #4	Results	"well in utero surgeries can prevent elective abortions of some fetuses, the ability to correct certain fetal conditions during pregnancy may consequently exacerbate negative views in society and developmental and physical disabilities." This is a provocative statement that really necessitates further explanation within the text	We have revised the sentence to be clearer.
Peer Reviewer #4	Results	what is "imminent hydrops"?	This is the terminology used by the authors but it is not defined in the paper, as we have noted in the text.
Peer Reviewer #4	Results	"mirror hydrops" should more appropriately read "MIRROR syndrome (a form of severe preeclampsia)".	Change made.
Peer Reviewer #4	Results	You state "developed an oxygen requirement", do you really mean pulmonary edema? If so, you should state	The authors report that the patient had an oxygen requirement that was

		it as such.	resolved with diuresis, not pulmonary edema. We have added in the text that the issue was resolved with diuresis to clarify.
Peer Reviewer #4	Results	For cases in which there was fetal urine production diagnostic testing of fetal urine did not clearly segregate those who would do well without intervention or outcomes of intervention." This is incorrect, please refer to Johnson MP, et al. Sequential fetal urine analysis provides greater precision and evaluation of fetal obstructive uropathy. Am J Obstet Gynecol 1995; 173(4):1334-1336.	We have added the reference to this paper, which was taken into consideration in the initial draft, and added selected diagnostic test characteristics to the text. The range of sensitivity for urine markers for predicting "absence of significant underlying renal damage" from last urine specimen obtained was 0.88 to 1.00; specificity from 0.47 to 0.84, with positive predictive values between 0.47 and 0.77. Given small sample size and the corresponding width of confidence intervals that would be expected around the individual diagnostic test characteristics, the level of ability to discriminate outcomes is modest and still a candidate for research.
Peer Reviewer #4	Results	you state: "there are currently no long-term data available to assess maternal risks both in immediate postoperative period (not true, please refer to reference #107) and related to longer-term fertility. (Again not true, please refer to: Wilson RD, et al. Reproductive outcomes following pregnancy complicated by maternal-fetal surgery. Am J Obstet Gynecol 2004; 191:1430-1436).	Thank you for providing this reference. The report text to which you refer is specific to surgery for myelomeningocele; however, the recommended paper does not distinguish outcomes for the women with this surgery in particular.
Peer Reviewer #4	Results	"… and a plurality of these go on to dialysis and transplant." I would disagree, and suggests you go back and read reference #137 which is the only long-term outcomes paper looking at true survivors of lower urinary tract obstruction. Actually, in that paper 44% had good renal outcomes, 22% had mild insufficiency	Thank you for the comment and detail in highlighting discordances, which was helpful as noted below. This section is specific to eight retrospective cohorts (Refs 124, 128-134) and does not include Biard et al (Ref 137). The

		not requiring dialysis, and only 34% required renal replacement. As such, one could argue that in 66% of survivors of vesicoamniotic shunting (> 90%), in utero therapy prevented severe renal injury (end-stage dysplasia).	majority of the studies had rates of renal compromise right at 50%: 4 of 8 (Salam; #128); 1 of 2 (Warne #130); 5 of 8 (Holmes #131); 3 of 6 (McLorie #132); and 1 of 2 (Harrison 124). Two studies, Crombleholme, 0 of 19 (#134) and Freedman 5 of 17 (#133), are notable exceptions and had high proportions of untreated fetuses likely indicating highly selective populations. In aggregate the risk of renal compromise is 30%, and the risk is "near 50% in most cohorts", with the plurality of those with renal function abnormalities did have renal failure/transplant/transplant eligibility. However, to avoid misinterpretation and improve clarity, we have modified the sentence to read: "risk of renal compromise is 31% across all retrospective cohorts, with the majority of smaller cohorts closer to 50% (Table 14). Among those infants with renal compromise the plurality progressed to dialysis and transplant. (Across all studies this was 25 of those shunted with failure compared to 11 shunted reported as having renal insufficiency or abnormal renal function) when the specific categories were given. Unfortunately some studies group these together.) Without trials in uniform groups the number needed to treat to prevent cannot be properly estimated.
Peer Reviewer #4	Results	"Need for shunt repositioning…" Shunts CANNOT be repositioned, they can only be replaced as they become obstructed or displaced.	We have deleted this text.

Peer Reviewer #4	Results	how was "no lung development" to find? Was the subject is based on ultrasound appearance or an actual measurement to support volume hypoplasia?	The gist of this comment is not clear; the lack of lung development was noted, as defined by the authors, in their research reports. The decision to intervene must be made prospectively; in utero imaging (with or without 3-D volumetric assessment) would be the available approaches. No detectable lung development is noted to be a contraindication to intervention by authors in this literature.
Peer Reviewer #4	Results	Page 58 last line to 59 first lines: More than half of otherwise normal infants . did not recover normal renal function in childhood and the majority required dialysis and renal transplant." What is the reference for these numbers? Are you referring to infants that did not undergo fetal treatment? Please clarify because reference #137 of survivors of confirmed bladder outlet (urethral) obstructions would argue otherwise.	In tracing back the numbers we identified a potential source of differences in synthesis of this research data, especially with regard to renal outcomes. We identified a double counting of renal failure and renal transplant from the data in Table 5 of Biard (Ref #137) which was interpreted to mean 12 children had renal failure, rather than 6 with renal failure and 6 with transplant who were the same 6 children – this does substantively influence interpretation as noted by the reviewer. In re-review of the 15 studies, correcting for the double counting and restricting to only those studies with clear denominators for renal function status by group, 40 of 104 surviving infants/children (38%) were reported to have renal failure, renal insufficiency, or “abnormal renal function”. We have modified the summary in several places and appreciate the patience in pointing out there was a flaw in the summary.

Peer Reviewer #4	Results	this is poorly written and not quite accurate. Might suggest reworded in it to " The outcomes of prenatally diagnosed, uncomplicated survivors to term are generally good. However, those fetuses with large, avascular tumors have a high incidence of prenatal mortality from high output cardiac failure or spontaneous hemorrhage in two or rupture of the growing tumor."	We have changed this statement to read "…prenatal mortality from high cardiac output failure or spontaneous hemorrhage into or rupture of the growing tumor."
Peer Reviewer #4	Results	sentence needs to be reworded	We have reworded this sentence.
Peer Reviewer #4	Results	"… included descriptions of percutaneous decompression of (should add: " large macrocystic components of") the SCT."	Corrected.
Peer Reviewer #4	Results	the donor twin can have decreased renal perfusion (not "renal pathology") and reduce urine production…"	Thank you. We have corrected this section.
Peer Reviewer #4	Results	Obstructive uropathy section: whoever wrote this portion of the paper seems to have a very negative bias in an unclear understanding of the issues in support of literature for this disorder.	We have attempted to be as objective as possible. We hope that the revisions made to this section reflect our scientific approach to the data.
Peer Reviewer #4	Results	Page 57 to 58, last sentence and beginning of first paragraph of next page: a very negative bias towards data reported in reference #137, and the the numbers stated are incorrect 1. only 6/18 (33%) required dialysis and eventual transplant. 2. 11/18 (61%) have spontaneous voiding, while 3/18 use intermittent catheterization, and only 3/18 (17%) are catheter dependent. 3. 7/18 (39%) have p.r.n. inhaler managed asthma, and 5/18 (28%) and an increased frequency of upper respiratory infections compared to normal age-matched populations. 4. "The majority of children will have one or more surgeries for the condition that cause the obstruction."	Renal data: Among prospective case series three report on renal outcomes in a manner that allows data extraction: Craparo (#136) of 10 surviving infants 6 have renal failure with transplantation or pending transplant; 4 have normal renal function. Biard (#137) of 23 livebirths, 8 of 18 have "normal renal function", implying that 10 do not; 6 were noted to have required transplant, so 4 were counted among those with "abnormal renal function". Freedman (#139) of 14 participants

		Can you please defined " the majority of children" as I can't seem to find this in the referenced paper	included in their report, 5 had renal failure and 3 had "renal insufficiency". So, 17 of 42 infants had renal failure (after eliminating the double count of 6 individuals) or 40%. The sentence "more than half will have severe renal disease…" was Corrected. to "34 to 40%" to encompass both the two larger studies and the context of consistency "with those of smaller reports." Voiding function: Biard (#137) of 18 with longterm bladder outcomes: 3 combined catheterization and voiding, 3 catheterized only, and one had a vesicostomy, for a total of 7 of 18 without normal voiding. Freedman (#139) of 14: 4 combined catheterization and voiding and 2 catheterized only for a total of 6 of 14 without normal voiding. Therefore, from these studies alone the estimate is 41% without normal voiding. This is in the middle of the contextual range for all studies including smaller of "one quarter to nearly half." This summary was not modified. Pulmonary function: Biard (#137) of 18: 5 with recurrent pulmonary infection; 7 with asthma. Freedman (#139) of 14: 3 have recurrent pulmonary infections; 1 has asthma. We have separated this conditions now in the text to be more specific: 8 of 32 (25%) with recurrent pulmonary infections; and 25% with asthma controlled by inhalers. Edits: "…25% have recurrent pulmonary infections, and 25 % have asthma controlled by

			inhalers." Interventions The conditions associated with shunting in these studies and the larger literature include PUV, Prune Belly Syndrome, cloacal abnormalities,urethral atresia; each are associated with interventions after birth. We have retained the phrase "one or more surgeriesa…" The specific sentence does not have an associated reference.
Peer Reviewer #5	Results	Missing 't' in heart	Corrected.
Peer Reviewer #5	Results	Thoracic lesions: Not really lung compression but increased intrathoracic pressure and vessel compression leading to hydrops that is the problem	We have provided more detail about CDH lesions that may benefit from fetal surgery.
Peer Reviewer #5	Results	Add RFA	Added.
Peer Reviewer #5	Results	Delete'6'	Corrected.
Peer Reviewer #5	Results	TTTS: would add info on laser being good at reversing cardiac complications in recipient. No real mention of cardiac issues with recipient at all. Compared to other sections this is a little this given that it is the volume treatment of all fetal therapy	Although the potential for reversal of cardiac complications in the recipient is important to note, we did not find literature to address this issue in the review. We agree that treatment for TTTS is the most common in utero treatment, and have noted this in the text.
Peer Reviewer #6	Results	The statement that perinatologists have "extensive training inexperience in using ultrasound guided techniques andlaparoscopy, … perinatologists are leaders in the develomentand conduct of minimally invasive approaches:" is not entirelytrue. generally	This section is contentious with multiple perspectives contributing differing observations. Since none are based on empiric evidence, we have deleted the section from the report.

		pediatric surgeons have far greaterlaparoscopic training and other types of minimally invasivetraining than perinatologists in the US. Further, pediatricsurgeons have been responsible for many of the advances inminimally invasive fetal surgery (tracheal occlusion, rfa fortrap,etc)	
Peer Reviewer #6	Results	San francisco does cardiac interventions	Thank you - we have updated our document.
Peer Reviewer #6	Results	One of the ethical quandraries that may need to be broachedis the issue of self referrals. That is both a diagnosis group forfetal anomalies then does the procedures and the followup	Reference to self-referrals was added to the last paragraph of the section.
Peer Reviewer #6	Results	There is no mention of fetal surgery for twin reversed arterialperfusion sequence and I think that there should be a sectionon this as it is one of the most common fetal operationsperformed	The conditions of particular interest for this report included open fetal surgery and fetoscopic surgery and their comparison to postnatal surgeries. The treatment decision in question should be between actions taking during pregnancy and those taken after birth. In the case of TRAP, the decision to intervene is to rescue the pump twin, with no salvage mission for the acardiac twin. By birth, the pump twin would not need surgery. Therefore, the decision was made that TRAP was different enough from our target conditions as to not fit in the report.
Peer Reviewer #7	Results	“Certain operations” instead of “Certain surgeries”	Thank you for your suggestion. We agree that the word “surgeries” can be imprecise. Therefore, we have changed the term to either operations or surgical procedures throughout the document.

Peer Reviewer #7	Results	same (‘operations’ instead of ‘surgeries’)	Thank you for your suggestion. We agree that the word “surgeries” can be imprecise. Therefore, we have changed the term to either operations or surgical procedures throughout the document.
Peer Reviewer #7	Results	the European body is called Eurofoetus, not Eurofetus	Corrected.
Peer Reviewer #7	Results	operations instead of surgeries	Thank you for your suggestion. We agree that the word “surgeries” can be imprecise. Therefore, we have changed the term to either operations or surgical procedures throughout the document.
Peer Reviewer #7	Results	quibble, maybe: perinatologists are certainly masters ofultrasound-guided techniques, but laparoscopy is asmuch the realm of pediatric surgeons as gynecologists –although often NOT obstetricians and MFM specialists.It is probably fair to say that, historically, it is thegynecologists who initially taught both perinatologists(for in utero interventions) and surgeons(appendectomies, cholecystectomies).	This section is contentious with multiple perspectives contributing differing observations. Since none are based on empiric evidence, we have deleted the section from the report.
Peer Reviewer #7	Results	Boston: Brigham and Women is affiliated with BostonChildren’s Hospital, not with Mass General – BostonChildren’s and Brigham together man the AdvancedFetal Care Center – the two rows should probably bemerged.	Corrected.
Peer Reviewer #7	Results	It is clearly NOT Children’s Hospital Boston of St.Elizabeth’s Medical Center; these are two separatehospitals (very separate)	Corrected.
Peer Reviewer #7	Results	The distinction between clinical affiliation and affiliatedhospital is strange and a little artificial – see Boston,Columbus, OH, New York	This distinction is necessary for some institutions (e.g. Rex Hospital).

Peer Reviewer #7	Results	The hospital affiliations for Brown are HasbroChildren's Hospital AND Women & Infants' Hospital ofRhode Island	Corrected.
Peer Reviewer #7	Results	not to be too self-promoting, but another reference (and more recent than 1987) is Luks FI, Carr SR, Feit LR,Rubin LP. Experience with a multidisciplinary antenataldiagnosis and management model in fetal medicine. JMatern Fetal Neonatal Med 2003;14:333-7. The modeldescribed herein was also held up as one of the idealmodels at the NIH Workshop on the future of fetaltherapy held in 2004 (see Chescheir N et al in ObstetGynecol)	Thank you for identifying this reference. We have added the reference to this section.
Peer Reviewer #7	Results	to imply that "the surgeon [needs to be prevented from] being the sole decision-maker (because of obvious conflicts of interest) sounds one-sided, as it seems to distinguish between surgeon and perinatologist (I assume that the authors meant 'surgeon' in a more generic way). Better would be "the surgical team" or the "interventionalists"	This sentence was edited to clarify that this is a recommendation for the informed consent process that was made in the ethics literature.
Peer Reviewer #7	Results	I don't believe that any of the 3 papers cited really suggest that animals are now used for preclinical training, much less to determine how many lab procedures need to be done before achieving proficiency. Most, if not all (large) animal models are currently used for research purposes, and often by individuals other than those who will perform clinical operations. Of course, it doesn't help that there is currently no good animal model for the most common of fetal operations, laser ablation for TTTS. There is, however, a precedent: in ECMO centers, particularly where case volume is limited, the team often maintains proficiency by using the animal lab for refresher courses (newborn lamb).	At least three publications, which we cite, note the role of animal models in development of surgical models and in training. We have edited the language to acknowledge that not all models are large animal models, and that while many centers have animal labs, just "some" actively use these facilities for surgical training.

Peer Reviewer #7	Results	I don't agree with this seemingly arbitrary number for proficiency: we presented a meta-analysis at last year's IFMSS (paper accepted for SMFM 2009 meeting, but voluntarily withdrawn after the controversy regarding previously presented work) showing that there was NO difference in outcome between centers havingperformed fewer than 40 cases and those with more than 40 cases. While it makes perfect sense that a learning curve exists, the 50-to-75 number (and, in particular, the 20-40/year) is totally arbitrary and automatically excludes three-quarters of all centers cited in table 3 from expert status	We have deleted the reference that came from personal communication; the other numbers are based on published data so they remain.
Peer Reviewer #7	Results	"experts" may have an interest in limiting the number of centers; combined with this arbitrary learningcurve/numbers statement, quoting these experts without offering an opposing view sounds biased. To my knowledge, there is no objective difference in reported results between high- and low-volume centers (of course, bad results may not have been reported)	We have added a statement that empiric evidence does not exist but that expert opinion and analogous data from other surgical disciplines does connect volume and outcomes.
Peer Reviewer #7	Results	Determining expertise or regional center status does not HAVE to depend solely on individual case volume: theLeapfrog Initiative uses a different model to evaluatehigh- and low-prevalence conditions: for cardiac bypasssurgery, for example, the actual number of bypasses isimportant; for low volume conditions, such ascongenital anomalies, the overall size of the NICU andthe available resources are measures of excellence, NOTjust the number of individual cases (of CDH, forexample). For fetal surgery, the presence of key playersand an overall volume threshold may be more relevantthan the actual number of bladder shunts placed annually.	This is a very good point. We have added these other considerations to the text.
Peer Reviewer #7	Results	'operations,' not 'surgeries'	Thank you for your suggestion. We agree that the word "surgeries" can be imprecise. Therefore, we have changed

			the term to either operations or surgical procedures throughout the document.
Peer Reviewer #7	Results	Ethics: should there be a mention of “wrongful life”litigation, whereby a child may sue for having been bornwith a deformity (as a result of fetal intervention), ratherthan not having been born at all?	This is an interesting point, but it is one that did not emerge in the literature on the ethics of maternal-fetal surgery that we reviewed for this report.
Peer Reviewer #7	Results	“critical aortic stenosis with impending hypoplastic leftheart:” so stated, it gives the impression that we knowthat untreated aortic stenosis leads to HLHS – which isfar from proven. The relationship is further qualified(“…believed to be from underuse…”), but themechanism is too speculative not to be questioned moreclearly	We have revised the text to note that the relationship is hypothesized.
Peer Reviewer #7	Results	“All of these conditions, if untreated, are lethal:” This isa somewhat misleading statement: I assume it means‘any treatment,’ including postnatal – but the casualreader may understand that these lesions are all lethal if untreated in utero, giving the impression that fetal surgery is the only possible hope for these infants.	We have clarified the statement to include postnatal treatment.
Peer Reviewer #7	Results	“…with a biventricular circulation compared to..:”should be ‘compared with,’ or better yet, ‘and’ – sincethis is not a comparison between two groups, but 2possible outcomes within the same group; and “stillborn” should be ‘stillborn’	We have revised this sentence.
Peer Reviewer #7	Results	the difference between 6/14 (42%) HLHS in theintervention group and 6/10 (60%) in the control groupis clearly not significant (P=0.36). The entire paragraphis (appropriately) critical of the claims, but should noteven acknowledge a “difference” in HLHS between thegroups	We have revised the text to note the lack of statistical significance in the observed difference.
Peer Reviewer #7	Results	Incomplete sentence?	Added the word "were" to correct this sentence

Peer Reviewer #7	Results	The summary focuses only on the feasibility of in uterocardiac intervention, but should devote an important(and cautionary) part to the physiological and embryological basis of it – i.e. the need for animal andother experimental models, better controlledobservational studies and, as has been put forth by theData Monitoring and Safety Committee of the BostonChildren's study, a well-controlled comparative studybetween in utero treated patients and postnatally treatedinfants	Added.
Peer Reviewer #7	Results	a very important (the most important, in fact) reason forimproved survival of CDH in the last three decades is abetter understanding of lung physiology in these infants:use of delayed diaphragmatic repair, better ventilatorystrategies, permissive hypercapnia, recognizing theimpact of stress and barotrauma, as well as significantimprovement in NICU technology (ECMO, nitric oxide,etc.)	Added statement to include these trends in care that improve survival.
Peer Reviewer #7	Results	it is now very well recognized that it is not mere "build-up of lung secretions… and [gradual distension]" that explains the success of tracheal occlusion, but that stretching of the future alveoli in late gestation lungs triggers cascades of accelerated lung growth and maturation, including increased DNA synthesis, epithelial and endothelial proliferation, increased phospholipid metabolism and surfactant synthesis.	We revised this section.
Peer Reviewer #7	Results	Strange sentence structure	Revised; thanks.
Peer Reviewer #7	Results	"Fetendo" is a(n unfortunate?) neologism used for anyform of Fetal Endoscopy (any endoscopic approach tothe uterus); this includes the placement of metal clips onthe trachea through endoscopic dissection of the fetalneck. The current technique uses fetal tracheoscopy andplacement of a detachable balloon – a more advancedform of fetal endoscopy. If it is	We have changed the text to use "fetal endoscopy."

		absolutely necessary, Iwould spell it FetEndo.	
Peer Reviewer #7	Results	the untreated control group in Europe, with 11%survival, can only serve as an ongoing reference point inEurope, NOT in the United States, where postnataltreatment results in many (although not all) centers farexceeds these figures.	Noted - we have indicated this in the text
Peer Reviewer #7	Results	It is somewhat incorrect that “multiple centers areworking on device development for an improvedballoon:” in fact, the previously used balloon(Detachable Silicone Balloon, or DSB, from BostonScientific) is no longer available from that, or any othercompany (a start-up, StarFire Medical, was not able todistribute it) because of commercial considerations; theballoon currently used in Europe is not yet FDA-approved in the States, but two centers (UCSF andBrown) currently have an Investigational DeviceExemption to use that balloon for fetal trachealocclusion purposes.	Thank you for clarifying. We have added the words “or approval process” after “device development” to clarify.
Peer Reviewer #7	Results	MMC is the most common ‘form’ of spina bifida, ratherthan ‘cause’ of spina bifida? One does not cause theother	Corrected.
Peer Reviewer #7	Results	the description of the balloon may lead to confusion: itIS a specialized balloon, but only to the extend that itwas specially designed for vascular embolization. It wasnot designed for tracheal occlusion and its use in fetalsurgery is off-label.	Thank you - we have changed the text to reflect this and to be more clear.
Peer Reviewer #7	Results	“…specific anomalies OF THE disease process” (ratherthan ‘and’)	Corrected.
Peer Reviewer #7	Results	needs name in full first: Management OfMyelomeningocele Study (MOMS)	The study name is spelled out for the first time on page 17.

Peer Reviewer #7	Results	confusing sentence: “In this case when there is renal function and a ureteral impass?” Better: “In case of unilateratal ureteral obstruction (and normal urine production), only the upstream portion of the urinary system is distended”	Thank you - we have changed the wording per your suggestion.
Peer Reviewer #7	Results	The entire paragraph on the ‘physiology’ of amnioticfluid is a little difficult to follow, and there is at least onemistake: the fetus does not ‘breathe’ amniotic fluid;rather, the presence of amniotic fluid allows stenting ofthe tracheobronchial tree, insofar as the flow of lungfluid meets some resistance and therefore distends thelungs (which triggers lung development, see aboveunder CDH); in addition, fetal breathing movements,which are episodic movements of the fetal chest wallthat modulate lung growth, is impaired inoligohydramnios, because of the physical compressionof the fetus inside the uterus.	We have clarified the text.
Peer Reviewer #7	Results	The summary talks a lot about indications, lack ofrandomization, long-term outcome as well as survival –but no discussion about techniques, or ultimate goal ofintervention. If there is no real difference in renal failurebetween treated and untreated patients, the main reasonto treat is to correct oligohydramnios and prevent lethalpulmonary hypoplasia. The simplest approach isvesicostomy (double pigtail catheter), but dislodgementis common (not discussed in this review). Open vesicostomy is more secure, but is associated with much higher morbidity/mortality for mother and fetus – although one group has recently looked again into open fetal surgery for LUTO. Fetal cystoscopy and ablation of urethral valves is the most recent, and least validated method; the potential for damage to adjacent structures and the completely unknown long-term effect of fetal cystoscopy and urethroscopy have to be stressed – few, if any, pediatric urologists have been consulted or involved in these prenatal procedures, which have all been described by obstetrical groups.	We have strengthened information regarding the lack of randomized trials making direct comparisons of techniques to inform choice of intervention and limited understanding of long term outcomes. Within the Obstructuve Uropathy section we had noted that shunt replacement is common .

		Finally, this review only briefly mentions the greatest stumbling block of all: accurate selection of patients, which has to hinge on prediction of renal function (intervention to restore amniotic volume is futile if renal function is too far advanced and the fetus doesn't produce enough urine). Urinary electrolytes from (repeated) bladder aspirates, ultrasound appearance of the kidneys and beta-2 microglobulin, among other parameters, have proven to be insufficient to accurately predict postoperative renal function.	
Peer Reviewer #7	Results	mirror syndrome is usually associated withplacentomegaly as well – the latter is a known riskfactor for pre-eclampsia	Thank you - we have added this information to the text.
Peer Reviewer #7	Results	at least two cases of radiofrequency ablation with neonatal survival were associated with severe damage to the infant's perineum (as reported at an international meeting by the team treating the newborn, not the original fetal surgery team.	We do not find these cases reported in the literature that met inclusion criteria for this review, but thank you for pointing these out to us.
Peer Reviewer #7	Results	"distortions of normal anatomy" (poorly phrased?), iftemporary and before 26-28 weeks, typically do notimpair lung development that much. The biggestconcern (and main reason to intervene) is compressionof the mediastinum, impairing venous return and therebycausing cardiac failure (hydrops). Most lesions do notcause hydrops, and an even smaller minority ends upcausing such prolonged pulmonary compression as tolead to pulmonary hypoplasia at birth	We have changed the text to note: "Only a small subset of patients with congenital pulmonary airway malformations are candidates for in utero treatment. In this subset, the mass is large enough and in such an anatomically-critical position that the fetal mediastinum is compressed, leading to impaired venous return with resulting fetal hydrops secondary to cardiac failure. When this occurs early enough in gestational age that delivery and post-natal treatment are not an option, in utero treatment is a possible solution. The majority of CPAMs however do not have an indication for prenatal treatment as the outcomes are

			excellent, often times with the tumors regressing throughout pregnancy and causing no neonatal or early childhood symptoms. Often times the more difficult judgements to be made during pregnancy are the frequency with which these tumors should be monitored in order to detect the small percentage that will cause fetal harm in order to know when to intervene.
Peer Reviewer #7	Results	I strongly disagree that “BPS is likely to be very rare.”In fact, it is at least as common as pure CCAM in many centers’ experience, and includes pure thoracic, intra-abdominal and mediastinal/peridiaphragmatic lesions. They tend to be small and asymptomatic at birth and therefore only detected if a prenatal diagnosis had been made. In most centers with active prenatal diagnosis, the incidence of BPS has therefore increased substantially in recent years	We have changed the text to note that "distinguishing between these conditions is difficult and some would argue clinically irrelevant until after birth. The final common pathway that leades to consideration of fetal intervention is the same--fetal hydrops--whether the lesion is considered a pure CCAM, BPS, or a hybrid lesion. Evaluation of 40 infants classified as having BPS found 50 percent of infants had elements of CCAM on their lung pathology. The diagnosis of CCAM is likewise not always certain until after surgery. In separate series four of 33 suspected CCAMs had BPS upon pathologic exam; six of nine had “hybrid lesions”(CCAM and sequestration present in the same lesion), and 16 of 37 were lesions other than CCAM. ."
Peer Reviewer #7	Results	a more current name for thoracic lesions is CongenitalPulmonary Airway Malformation (CPAM), whichregroups both CCAM and sequestrations (andrecognizes how common hybrid lesions are, or CCAMswith feeding vessels). I would consider either changingit, or at least noting this upfront.	Thank you. We have changed the text to reflect the correct name.

		I would be very cautious about mentioning the steroidpaper (and trial) in the Summary – this is far from beingaccepted as even a rational concept, never mind a study.Indeed, the proposal for a multicenter NAFTNet study isno longer alive.	We have revised the text.
Peer Reviewer #7	Results	I disagree with the statement that "[Greater than 90percent] of pregnancies…presenting with TTTS prior to26 weeks will end with [dual fetal demise]" – thatnumber needs to be better qualified: most pregnancies(but probably not greater than 90%) with severe ANDworsening TTTS will end in dual demise. There are atleast 2 studies showing that the progression of TTTS isnot only not linear, but is as likely to improve as toworsen from week to week (Luks FI, Carr SR, PlevyakM, Craigo SD, Athanassiou A, Ralston SJ, Tracy TF Jr.Limited prognostic value of a staging system for twin-to-twin transfusion syndrome. Fetal Diagn Ther. 2004May-Jun;19(3):301-4 and O'Donoghue K, Cartwright E,Galea P, Fisk NM. Stage I twin-twin transfusionsyndrome: rates of progression and regression in relationto outcome. Ultrasound Obstet Gynecol. 2007Dec;30(7):958-64.)	Changed the statement to indicate that "Greater than 90 percent of pregnancies presenting with severe TTTS and not undergoing some sort of therapy will end with dual fetal demise."
Peer Reviewer #7	Results	in general, there is not enough emphasis on the fact thatthe vast majority (more than 67%, and probably morethan 80%) of prenatally diagnosed CPAMs regresspartially or completely by the third trimester, and thatonly a small fraction requires intervention – and also,that the biggest problem with this (and many other fetalsurgery indications) is poor prognostic indicators. ForCPAMs, the most commonly used criterion is the mass-to-chest volume ratio, similar to the LHR in CDH. Thatcriterion, developed by Crombleholme et al, seems bestable to predict the risk of developing hydrops.	We have added an emphasis on the limited utility of prognostic indicators and emphasized that only a small subset of fetuses with CPAM are candidates for treatment.

Peer Reviewer #7	Results	septostomy was one of the treatment options, based onthe ASSUMPTION that fluid equilibration would occurbetween the two sacs. It has since been shown thatseptostomy does not work, i.e. that septostomy withamnioreduction of the recipient sac is no better thanamnioreduction alone (Cochrane review, Ultrasound Obstet Gynecol. 2008 Jun;31(6):701-11). Although septostomy continues to be mentioned in most introductions of TTTS papers, it has not been reported as a stand-alone mode of treatment since 2005	We have changed the text to note that septostomy is no longer considered a stand-alone treatment.
Peer Reviewer #7	Results	it is incorrect that both RCTs required amnioreduction prior to enrollment. Only the Crombleholme study did so. The Senat (Eurofoetus) trial randomized patients to either amnioreduction or laser PRIOR to any intervention.	We have corrected the text
Peer Reviewer #7	Results	It is important to indicate that the conclusion that stageIII and IV recipients fared significantly worse after laserthan after amnioreduction is based on a total of 8 and 12patients, respectively. The difference in mortality (30%vs. 70%) is in fact 30% vs. 65%, and a chi-square test onthat shows a P of 0.06 (the quoted 0.03 is for a 1-sidedchi-square, which would assume knowledge that oneapproach is superior than the other – clearly notapplicable here)	We have rewritten that paragraph to more precisely reflect the study results.
Peer Reviewer #7	Results	Crombleholme study incorrectly labeled as UK, insteadof USA	Corrected.
Peer Reviewer #7	Results	again (see comments for page 16), the literature does notsupport the importance of very stringent techniques ofmapping the vessels, as different centers use differenttechniques (including selective vs. not-so-selective) withvery similar results. This is not to say that techniquesshould be lax, and the checks and balances comment isvery important – but there is no scientifically accurateproof that one particular technique is superior	We have added a statement to remind readers that the basis for stringency and type of mapping techniques are not well evaluated in the empirical literature and likely warrant further study.

		(with thepossible exception of sequential laser occlusion (AVfrom donor to recipient first, followed by the othervessels) – but this has only been reported by one author,and has not yet been validated by others.	
Peer Reviewer #7	Results	Technically, there are only 3 published randomizedtrials – but the sentence, as it stands, suggests theEXISTENCE of RCT – in that case, the MOMS trialshould probably be added	Thank you for pointing out the lack of clarity. We have added the word "published."
Peer Reviewer #7	Results	Baltimore, Chapel Hill, New York and Phoenix ARENAFTNet members; Dallas and Pittsburgh (not in yourtable) are NAFTNet members as well – not sure howmuch they already do in terms of fetal intervention.	Corrected.
Peer Reviewer #8	Results	No comment	
Peer Reviewer #9	Results	Did you really mean fourth paper?	Yes, Corrected. Thank you.
Peer Reviewer #9	Results	left instead of right	Corrected.
Peer Reviewer #9	Results	microcolon misspelled	Corrected.
Peer Reviewer #9	Results	six6	Corrected.
Peer Reviewer #10	Results	3 "certified fellows" now at CHOP.	Corrected.
Peer Reviewer #10	Results	stent placement is used for fetal obstructive uropathy treatment, not TTTS.	Corrected.
Peer Reviewer #10	Results	I do not agree with this statement. It is crucial that the responsible surgeon obtain operative consent from the mother, preferably in the context of counseling by individual team members as well as a preoperative	We clarified this sentence to reference the ethics literature, which this section reviews.

		team meeting with family. That is the format used for the MOMS Trial patients for example	
Peer Reviewer #10	Results	The authors should point out that the high mortality of HLHS and intact atrial septum is the pulmonary vasculopathy that develops before birth.	We have added this observation.
Peer Reviewer #10	Results	fetal thoractomy and laparotomy (the "two step" approach).	This comment is unclear, and we could not locate a relevant reference to the approach. Therefore no change was made.
Peer Reviewer #10	Results	lung growth, not lung maturation.	Corrected.
Peer Reviewer #10	Results	The survival of infants with LHR greater than 1.0 was not 100 percent.	Thank you - we have revised the text to delete this sentence and to indicate that survival was greater in both groups for infants with LHR >0.90.
Peer Reviewer #10	Results	A comment should be made that reported outcomes for postnatally treated infants with CDH in Europe show a much lower survival rate than the results reported from major centers in the US	We have added a comment about the difficulty of reconciling rates across centers.
Peer Reviewer #10	Results	Exclude the comment regarding aseptic surgery!!	We have simplified the text.
Peer Reviewer #10	Results	Statement is not true. Studies from UCSF and from CHOP have reported the effects of open fetal surgery on subsequent maternal morbidity and subsequent fertility.	Again, we thank you for pointing this out. We did not find specific data in our included studies for this section; however, we have changed the text to "little data" rather than "no data."
Peer Reviewer #10	Results	Statement not true regarding the etiology of oligohydramnios induced pulmonary hypoplasia.	We have clarified the statement.
Peer Reviewer #10	Results	A general comment: in appropriately selected fetuses with urethral obstruction and oligohydramnios, placement of a vesicoamniotic shunt may reverse	Thank you for this comment; the text stresses that long term renal outcomes are not well understood.

		oligohydramnios and prevent pulmonary hypoplasia but the effect of fetal treatment on future renal function is unclear.	
Peer Reviewer #10	Results	The pathognomonic feature of a fetal pulmonary sequestration is an arterial feeding vessel from the systemic circulation, but an intralobar sequestration will also have pulmonary blood supply.	We have changed the text to note that "BPS does not connect to airway and has blood flow from branches off the aorta as well as the pulmonary circulation"
Peer Reviewer #10	Results	hydrops (not impairment of fetal lung growth) is the indication for fetal treatment (also p 67, line 39).	We have clarified this section.
Peer Reviewer #10	Results	A "hybrid lesion" is defined as a CCAM and a sequestration present in the same lesion.	We have added this definition
Peer Reviewer #10	Results	Need to clarify the Stocker pathologic classification of CCAM.	We have clarified this section.
Peer Reviewer #10	Results	A tension hydrothorax is one etiology of hydrops from a BPS associated with a hydrothorax.	We have clarified this section.
Peer Reviewer #10	Results	Sentence does not make sense.	We have revised the sentence to be more clear.
Peer Reviewer #10	Results	The RCT for steroid treatment includes fetuses with large lesion but without findings of hydrops.	Corrected.
Peer Reviewer #10	Results	Which approaches are the authors referring to when they cite "both approaches".	We have modified the text to note that both selective and sequential approaches were associated with greater survival rates.
Peer Reviewer #11	Results	This opening paragraph should provide a more comprehensive account of the ethical issues that arise concerning maternal-fetal surgery. The first and perhaps foremost is that surgery on the fetus is also surgery on the pregnant woman. Hence, the importance of the use of "maternal-fetal surgery" has	We have revised the section by using the term "maternal-fetal surgery" as recommended. The other topics mentioned by the reviewer appear later in the section, so we did not add them to the paragraph.

		been emphasized in the literature. In addition to the ethical issues identified in the second sentence, fetal surgery also raises ethical issues about: (a) the responsible management of innovation and experimentation in surgery and surgically related subspecialties that does not come under the Common Rule definition of research; (b) the informed consent process for such innovation and experimentation; (c) the moral status of the fetus as a patient; (d) the nature and limits of the ethical obligation of pregnant women to take risks to their own life and health for the sake of clinical benefit for the fetal patient and/or future possible child; and (e) when fetal surgery should be offered or recommended to a pregnant woman. These issues should be added to the first paragraph.	
Peer Reviewer #11	Results	The second paragraph focuses on a controversy in maternal-fetal medicine: coerced cesarean delivery for fetal benefit. There emerged from this controversy court rulings that supported the right of a pregnant woman to refuse cesarean delivery and rulings that ordered ultrasound evaluation and, if a major complication such as intrapartum complete placenta previa were diagnosed, cesarean delivery. (In the Jefferson case from Georgia the placenta previa spontaneously resolved before the patient went into labor.) There also emerged differing positions in the ethics literature and also by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics on the relative weight that should be given to the autonomy of the pregnant woman in such cases. ACOG initially took the view that respect for the pregnant woman's autonomy was so important that coerced cesarean delivery was almost never justified. AAP placed more emphasis on the obligation of pregnant women to accept reasonable risks to themselves for the benefit of the fetus and future child. There was no support for routine coerced cesarean delivery. In this context, citing papers about	We have retained this paragraph because it adds historical context to what ethical issues were identified as the field of maternal-fetal surgery was developing. The section also is clear about why this discussion was eventually abandoned in the literature.

		the potential for compulsory fetal surgery is out of place, because this should now be regarded, ethically and legally, as unrealistic and therefore a purely speculative concern. Unless this paragraph can be very substantially changed, it would be better to delete it, as it is non-essential	
Peer Reviewer #11	Results	line 4 from bottom, after "a data and safety monitoring board" add "for IRB-approved research and by some other appropriate prospective review for innovation that is not yet research."	We have revised this sentence.
Peer Reviewer #11	Results	emotional "turmoil" is not the best word choice; "burden" might be better. There are also ethical challenges in the informed consent process and these should be separately acknowledged and not equated to emotional burdens.	Change made as suggested.
Peer Reviewer #11	Results	First full paragraph, first sentence: "to ensure the best outcome" is too demanding an ethical standard in a still-new clinical field. A better word choice would be "to continuously improve and asses the quality of outcomes."	This sentence was modified based on the recommendation but using different phrases.
Peer Reviewer #11	Results	First full paragraph, third sentence: We question the proposal that a "neutral but knowledgeable" clinician, "preferably not the surgeon" lead the consent process. It is well established in the ethics of informed consent that the clinician leading the process must be qualified to do so by reason of training, experience, and disciplined clinical judgment and decision making. For some fetal interventions this will be the obstetrician and for some it will be the pediatric surgeon. This physician must be aware the views of the entire clinical team and ensure that their perspectives are communicated to the pregnant woman. Moreover, this sentence cites a paper that is more than 20 years old and therefore was not informed by developments in surgical ethics in the	This sentence was edited to clarify that this is a recommendation for the informed consent process that was made in the ethics literature. The reference in the draft report was incorrect due to a formatting error and has been corrected.

		past decade, which included working out the ethics of the informed consent process for surgery when multiple physicians are involved in a patient's care.	
Peer Reviewer #13	Results	The suggestion that difference between European vs. USA fetal surgery programs is due the difference in training is questionable. The fact is the chronology of the use of fetoscopy (amnioscopy) for prenatal diagnosis and therapy from US and European centers parallel each other. OFurther as the authors note later in the manuscript the use of laser for twin twin transfusion syndrome was first performed in the US, by DeLia. Subsequent to this, as the European's began their fetoscopic programs, other US program, primarily in depts of Ob/Gyn also began working in the area. As the authors have stated, the initial "open" fetal surgery, lower urinary tract obstruction, was performed by pediatric surgeons, logically, this was a disease [along with CDH, CCAM, SCT and ONTDs] that they would be treating postnatally, not something that Ob/Gyn surgeons would treated in the neonate. This reviewer would suggest that the authors rethink the suggestion that the difference between European and US fetal programs is due to training.	This section is contentious with multiple perspectives contributing differing observations. Since none are based on empiric evidence, we have deleted the section from the report.
Peer Reviewer #13	Results	change "Baylor College" to "Baylor College of Medicine", they are two different institutions.	Corrected.
Peer Reviewer #13	Results	The authors should confirm if the CHOP fellowship is a "cinical fellowship (hands on) or an observational one. If it is the latter,this would mean at the present time there is only one formal "hands on" clinical fellowship in the country, the Baylor program.	The CHOP fellowship is clinical, and reports similar training characteristics.
Peer Reviewer #13	Results	As the manuscript is from VUMC the authors are aware that the surgical aspect of the NICHD sponsored MOMs Trial has been suspended at VUMC. This center is presently only doing follow up. How do the authors want to handle this?	We have corrected the table.

Peer Reviewer #13	Results	Please change sentence from "…agreed to a moratorium…" to "…agreed to moratorium within the United States…"	Change made.
Peer Reviewer #13	Results	Do the authors mean "All of these conditions, if untreated in utero, are lethal"? If so please add "in utero" or "prior to delivery".	We have changed the statement to read: "all of these conditions, if untreated either in utero or soon after birth, are lethal."
Peer Reviewer #13	Results	Change "babies" to "fetuses"	Corrected.
Peer Reviewer #13	Results	Do the authors want to make note that the fetal cases delivered on average 7 weeks earlier then the postnatally treated cases due to the develoipmen of PPROM in 100% of cases by 31 weeks. With no differnce in outcome, despite the preterm delivery in the fetal case, the findings suggested that there may be some benefit from tracheal balloon.	We have added this detail.
Peer Reviewer #13	Results	Under comparison groups for the Makin et al reference authors have written "varied interventions". Please list the interventions at the bottom of the table after "RFA"	Added.
Peer Reviewer #13	Results	Add "or cardiac decompensation." There are reported cases that suffered sudden IUFD prior to the development of hydrops who had significant increase in cardiac output.	Added.
Peer Reviewer #13	Results	Change "infants" to "fetuses"	Corrected.
Peer Reviewer #13	Results	Change "infants" to fetuses"	Corrected.
Peer Reviewer #13	Results	Delete "through NAFTNet". The study was presented at NAFTNet and was not approved by the Steering committee, at present there are 3 or 4 Centers, all are NAFTNet affiliates, participating in study, but it is	Corrected.

		outside of NAFTNet.	
Peer Reviewer #13	Results	Change "the shared placenta" to "intertwin placental vascular anastomoses (or communications)". Would suggest the authors change the sentence to "…the donor becomes hypovolemic resulting in reduce renal perfusion which may result in renal pathology, thus reducing urinary output and amniotid fluid volume in the donor twin's amniotic sac (oligohydramnos)". Point being, all have reduced perfusion/urinary output but its not clear if all have renal pathology.	Thank you. We have changed the text to reflect your suggestions.
Peer Reviewer #13	Results	Would suggest the authors change the sentence to "…conversely, is hypervolemic with increased renal perfusion resulting in polyhdramnios"	Thank you for the suggested wording - we have changed the text per your suggestion.
Peer Reviewer #13	Results	Add reference for Quintero staging sited above (line 110 of excel spreadsheet)	Reference added.
Peer Reviewer #13	Results	Change to"Demise of one or both twins"	Change made as suggested.
Peer Reviewer #13	Results	Change "disrupted" to "punctured"	Corrected.
Peer Reviewer #13	Results	Delete "to avoid pulmonary hypoplasia"	Corrected. as suggested
Peer Reviewer #13	Results	Change "placenta" to "uterus", access to the placenta for laser ablation is the same in all centers, it fetoscopic, how one gets to the uterus may vary amongst centers	Corrected.
Peer Reviewer #13	Results	Change "…and both required that pregnancies first have an amnioreduction prior to randomization." to…"one center required that pregnancies have an amnioreduction prior to randomization and the other considered previous invasiver therapy for TTTS an	We have corrected the text.

		exclusion criteria". Crombleholme et al require AR, Senat exlcuded if AR performed.	
Peer Reviewer #13	Results	Recognizing that the authors' last search of Pubmed was in January 2009 they would not have seen the most recent report from the Poissy group [Lenclen R, Caiario G, Paupe A et al. Neurodevelopmental outcome at 2 years in children born preterm treated by amnioreduction or fetoscopic laser surgery for twin to twin transfusion syndrome: comparison with dichorionic twins. AM J Obstet Gynecol 2009 Jul (doi:10.1016/j.ajog.2009.05.0360. While this report is beyond the window that the authors included in the methods, they may want to consider its additional as it does address the very concerns that they have raised the void of comparision groups	Thank you for pointing out this reference; as noted, it is beyond the current scope of the report.
Peer Reviewer #13	Results	Add "o" for "of laser"	Corrected.
Peer Reviewer #13	Results	Fetal surgery via telemedicine; the authors may wantto include the following report on page 15[Quintero RA, Munoz H and Pommer R et al. Operative fetoscopy via telesurgery.Ultrasound Obstet Gynecol 2002 Oct;20(4):390-1 and (2)The original report on TTTS staging was not included, although referenced in the paper [Quintero RA, Morales WJ,Allen MH et al. Staging of twin-twin transfusion syndrome. J. Perinatol.1999 Dec;1999(8Pt1):550-5	We have added these references.
Peer Reviewer #14	Results	Table 3 (p11) seems incorrect, at least with regard to the NAFTnet centers – according to the website: https://www.naftnet.org/naftnetmembers/tabid/86/default.aspx NAFTNet Centers Baltimore, MD University of Maryland, Boston, MA Brigham and Women's Hospital, Chapel Hill, NC University of North Carolina, Cincinnati, OH Fetal Care	We have corrected the table.

		Center of Cincinnati, Columbus, OH Ohio State University, Dallas, TX Southwestern Medical Center, Detroit, MI Wayne State University Houston, TX Baylor College of Medicine - Texas Children's Hospital, Montreal, QC Montreal Fetal Treatment Program CHU Sainte-Justine Research Center, Nashville, TN Vanderbilt University Medical Center, New Haven, CT Yale University Medical Center, New York, NY Columbia University, Philadelphia, PA Children's Hospital of Philadelphia, Phoenix, AZ Phoenix Perinatal Associates, Pittsburgh, PA Magee-Womens Hospital of the University of Pittsburgh Medical Center, Providence, RI Brown Medical School - Fetal Treatment Program, San Francisco, CA University of California, San Francisco, Seattle, WA Evergreen Hospital, Toronto, ON University of Toronto – Hospital for Sick Children – Mt Sinai Hospital, Vancouver, BC University of British Columbia	
Peer Reviewer #14	Results	The "formal fellowships" described on page 15 (or p22 of 106) – who or what entity oversees these fellowships. By describing them as "formal fellowships" it suggests that there is a group that accredits and oversees these fellows and that a process is in place to evaluate and certify them. I am not certain this is the case.	You are correct - we have deleted the word "formal."
Peer Reviewer #14	Results	The "formal fellowships" described on page 15 (or p22 of 106) – who or what entity oversees these fellowships. By describing them as "formal fellowships" it suggests that there is a group that accredits and oversees these fellows and that a process is in place to evaluate and certify them. I am not certain this is the case.	You are correct - we have deleted the word "formal."
Peer Reviewer #14	Results	No comment	

Public Reviewer #1	Results	Page tn and page 16 mention procedures that are done once and refers to them as one-off instead of one-of.	The word "one-off" is jargon and we have changed it.
Public Reviewer #1	Results	Page tn and page 16 mention procedures that are done once and refers to them as one-off instead of one-of.	The word "one-off" is jargon and we have changed it.
Public Reviewer #1	Results	states that the cardiac defects mentioned are "all fatal" then they go one to review the mortality which is not 100%	We have deleted the sentence suggesting that these conditions are always lethal.
Public Reviewer #3	Results	Some sections have summary and some do not. Please create a summary of findings for each type of defect/surgery described.	Added.
Public Reviewer #3	Results	it is helpful to have policies for key insurers (Table 5), but need each state's policies for Medicaid as this is the largest single insurer of pregnant women in the country, covering over 40% of all births. It would also be very helpful to have a detailed description of what is covered in other countries along with the clinical practice guidelines, studies underway, etc. from other countries.	We attempted to find each state's policies on line, but were unable to do so. Unfortunately, to research the policies at this level is beyond the scope of this project.
Peer Reviewer #9	Discussion/ Conclusions	of, second to last word	Corrected.
Peer Reviewer #10	Discussion/ Conclusions	Misses other publications from UCSF and CHOP in which maternal outcomes are delineated after maternal-fetal surgery	We did not locate additional papers from this group meeting inclusion criteria.
Peer Reviewer #14	Discussion/ Conclusions	The description of gaps on page 69 (76 of 106) includes “near absence of maternal outcome assessment is especially concerning (lines 50-51)”. This section needs to be expanded with more information and emphasis on the need for evaluation of reproductive outcomes for the mother. Given that fetal interventions are being performed for non-lethal	Thank you - we have added an additional emphasis on the need to study women's future reproductive health.

		anomalies and the impact that fetal surgery may have on long term reproductive function these outcomes critically need to be documented. It is not uncommon for the fetal surgery to be performed at 22-25 weeks, preterm labor to occur at 28 or 30 weeks resulting in a cesarean delivery with two uterine procedures within a month of each other on a preterm uterus, the impact on the mother's future reproductive health needs to be an integral part of the consenting process. Similarly, does this impact her future long term health – are there more adhesions that may make subsequent surgeries more difficult?	
Peer Reviewer #14	Discussion/ Conclusions	Page 71 (page 78 of 106) future research directions needs to include future maternal reproductive health as well as future maternal health. These are key future research needs. There needs to be an assessment that evaluates if fetal intervention shifts the fetal condition which may likely be lethal into a condition that results in a severely disabled child.	Thank you - we have added an additional emphasis on the need to study women's future reproductive health.
Public Reviewer #3	Discussion/ Conclusions	Felt that the discussion section was too brief. Recommendations for policymakers and researcher need to be included. This is a complicated field, but policymakers are asked to make decisions with quite little evidence to guide decisions. Trying to give interim guidance for them or at least giving factors they might consider would be useful. If, for example, the research team feels that a particular procedure should be restricted to trials only it would be helpful to say so.	As an AHRQ-funded Evidence-based Practice Center, we are contracted to evaluate the current state of the literature and practice for this technical brief. Our role is to evaluate the current state of the literature (and of practice, for technical briefs) so that other organizations, including professional groups, can use our reports as they deliberate and develop guidelines. It is, however, beyond the scope of the EPC program to provide prescriptive guidance.
Peer Reviewer #6	General Comments	Overall, this is an excellent state of the art on maternal fetal surgery and one of the best reviews of the subject that I have had the opportunity to review. I appreicate the investigators time, effort and diligence in preparing	Thank you

		this report	
Peer Reviewer #11	General Comments	It would be more effective and clinically relevant to frame the ethics of maternal-fetal surgery in terms of three major ethical considerations that shape the current literature on the topic: (a) the distinction between fetal intervention that has emerged as standard of care or at least widely accepted, e.g., intervention to manage twin-twin transfusion syndrome, and fetal intervention that is research, such as the MOMS trial, or that is innovative but not yet research, such as in utero surgical removal of sacrococcygeal teratoma; (b) the pregnant woman's right to make an informed decision about maternal-fetal surgery, which is a central consideration in all of obstetric care and should be given even greater weight in research and innovation in maternal-fetal surgery; and (c) the ethical obligation of the pregnant woman to accept risk to herself from maternal-fetal surgery, an obligation that becomes progressively less weighty as one moves along the continuum of accepted fetal intervention to research and to innovation that is not yet research. The report should also call for sustained and high quality investigation of the ethics of maternal-fetal surgery in the section on "Future Research" on page 78 or 106 (page 71 at bottom of page).	These are excellent points, but we are trying to provide a more historical and contextual overview of the ethics literature and debates rather than make specific claims about what should be considered the most important ethical consideration today.
Peer Reviewer #11	General Comments	For a still-developing field, isolated case reports have value. For example, complications may be reported in a case that do not recur in a subsequent case series from a center or in case series from other centers. Nonetheless, these complications could be clinically significant and therefore relevant to counseling a pregnant woman about maternal-fetal surgery. In addition, insights can be gained from review of case reports that then shape subsequent case series. A strong case therefore needs to be made for omitting case reports in such a new field.	Certainly, case reports can provide useful information, especially around harms or, as indicated, in the case of a new field. However, the decision was made to exclude single case reports because a) the number of studies available that included at least 2 cases was substantial and b) to review each individual case (many of which were already included in the case series reviewed) would have expanded the

			scope of work beyond what was feasible in the contract.
Peer Reviewer #11	General Comments	In any innovative, rapidly evolving field of clinical intervention, the intervention itself can rapidly evolve, making comparison of processes of intervention and their outcomes a challenge. This challenge should be acknowledged.	Added this challenge to the "Challenges and Opportunities" section.
Peer Reviewer #11	General Comments	As we read through the report we were impressed by the considerable variation in scientific quality, e.g., no consistent inclusion or exclusion criteria for some interventions, no long-term follow up, and no data on maternal outcomes. This variation in scientific quality is a challenge for maternal-fetal surgery and the report should emphasize the need, urgently, to address this challenge, e.g., by multi-center cooperation of the sort being fostered by NAFTNet in North America.	We feel that we have done so in the discussion and future research sections of the report.
Peer Reviewer #9	General Comments	The table of contenets needs to be re-numbered to accurately reflect the page numbers	The table of contents reflects the report pagination; however, additional page numbers are added in the process of uploading to manuscript central for review.
Peer Reviewer #9	General Comments	This compendium of procedures is an excellent resource for MFMs, pediatric subspecialists, fellows etc. However, if the idea to for other stakeholders (insurance companies, individual patients) use this as a resource, the format would need to have additional summary sections with condensed conclusions/recommendations.	The report will also be published in condensed format that should be of utility to multiple stakeholders.
Peer Reviewer #9	General Comments	I think from the beginning there should be statement that this is a meant as a status report of what is currently offered and a review of how thoroughly results from the studies have been published regarding things like long term neonatal outcomes, shortterm maternal complications and NOT that this report	Thank you for identifying this source of confusion. We have added text to clarify the intent of this report, which is, as you note, a status report.

		attempts to suggest best practices for managing the fetal conditions reported on. Under Key Question 1e, there really is really not an attempt to report the current state of which way the scale is tipping, with our current knowledge, for each procedure (which is OK if this is clearly stated from the beginning and we are not concerned with other uses of this report - see below.	
Peer Reviewer #9	General Comments	I think the authors should add a bulleted list under "state of the science" highlighting findings described in those 2 pages. And if, as suggested in the opening paragraph, "stakeholders requesting this report were specifically interested in instances in which strong comparative research suggests superiority of materna-fetal surgery over intervention at birth" have we really given them something to use? If this was the intent then more specific recommendations are needed for those groups to use as treatment guidelines. This would then create impasses where certain centers have required outside funding for the procedures and raises the question of funding for these procedures, many of which still remain experiemental or at least not clearly proven to be superior.	We have clarified in the report that although stakeholders are interested in questions of comparative effectiveness, the field is not evolved to the point that those can be answered. Rather, we have described the current state of the science, with suggestions about the trajectory of the field at this time.
Peer Reviewer #9	General Comments	I would not label the last section Future Research - as it really lays out guidelines for addressing current weaknesses in maternal-fetal surgery programs. A Future Research section could be used to lay out questions for future study.	We changed the title of this section to "Challenges and Opportunities."
Public Reviewer #1	General Comments	In every sentence where the text should have a / the word "of" is inserted. Dates then all read 4 of 07 of 2009 instead of 04/07/2009.	Corrected.
Public Reviewer #3	General Comments	References: see under section 2 methods comments re including more from rest of world	We have attempted to identify research ongoing internationally as well as in the United States.

Peer Reviewer #4	Tables	Table 3; University of Maryland, University of North Carolina - Chapel Hill, Columbia University in New York city, Phoenix. Gale Associates, are all NAFTNet affiliates.	Corrected.
Peer Reviewer #4	Tables	Wilson et al 2003: you need to go back and review the numbers, as what is listed in Table 14 make no sense. Are you trying to summarize his Table 2 or specific article(s) reference in this paper? Table lists 202 fetuses undergoing shunt placement from nine different case series, with an overall renal insufficiency rate of 46% in 63 reported survivors.	Corrected.
Peer Reviewer #4	Tables	Freedman et al 1996: again your numbers are incorrect. I assume you extracted these numbers from Figure 1? Actually, 5/27 (19%) of fetuses without fetal surgery **survived**, while 22/27 to fetuses died.	Corrected.
Peer Reviewer #4	Tables	Manning et al 1986: typo: G1 vesicoamniotic shunt number is (73).	Corrected.
Peer Reviewer #4	Tables	Bernaschek er al 1994: statement "29 shunts (for a broader range of conditions included in aggregate and paper) acquired shunt replacement", does not make sense. Especially when you're number of shunt patients a group 1 was 13. This sentence requires clarification.	Corrected.
Peer Reviewer #5	Tables	Maryland is in NAFTNET	Corrected.
Peer Reviewer #5	Tables	Brigham and Women's performs cardiac interventions with boston Children's	Corrected.
Peer Reviewer #5	Tables	Chapel Hill is NAFTNET member	Corrected.

Peer Reviewer #8	Tables	No comment	Corrected.
Peer Reviewer #9	Tables	description of comp. group for 1st entry	Corrected.
Peer Reviewer #10	Tables	2 Boston centers are not doing fetal intervention for CDH. Children's Hospital of Boston of St. Elizabeth's is a mistake. Fetal cardiac intervention has been performed at the Children's Hospital of Philadelphia.	Corrected.
Peer Reviewer #14	Tables	Table 3 (p11) seems incorrect, at least with regard to the NAFTnet centers – according to the website: https://www.naftnet.org/naftnetmembers/tabid/86/default.aspx NAFTNet Centers: Baltimore, MD University of Maryland; Boston, MA Brigham and Women's Hospital; Chapel Hill, NC University of North Carolina; Cincinnati, OH Fetal Care Center of Cincinnati; Columbus, OH Ohio State University; Dallas, TX Southwestern Medical Center; Detroit, MI Wayne State University; Houston, TX Baylor College of Medicine - Texas Children's Hospital; Montreal, QC Montreal Fetal Treatment Program CHU Sainte-Justine Research Center; Nashville, TN Vanderbilt University Medical Center; New Haven, CT Yale University Medical Center; New York, NY Columbia University; Philadelphia, PA Children's Hospital of Philadelphia; Phoenix, AZ Phoenix Perinatal Associates; Pittsburgh, PA Magee-Womens Hospital of the University of Pittsburgh Medical Center; Providence, RI Brown Medical School - Fetal Treatment Program; San Francisco, CA University of California, San Francisco; Seattle, WA Evergreen Hospital; Toronto, ON University of Toronto – Hospital for Sick Children – Mt Sinai Hospital; Vancouver, BC University of British Columbia	Corrected.
Peer Reviewer #3	Tables	The USFetus (Los Angeles, CA and USF, Tampa, now University of Miami), addresses all of the conditions	Corrected.

		mentioned in Table 3, with the exception of open fetal surgery for spina bifida (for philosophical reasons). The difference is the USFetus uses a minimally-invasive approach, not the open surgery approach.	
Peer Reviewer #3	Tables	The taxonomy used in Table 4 is a particular view of the field by an individual investigator, but not necessarily shared or approved by others. For example, a different classification of centers would be by volume, by results, by success, by the surgical approach.	We have added a statement in the text to reflect this.
Peer Reviewer #3	Tables	The section on CCAM, including Table 17, did not include our publication of percutaneous ultrasound-guided fetal sclerosis of these lesions (Bermudez et al. Percutaneous Fetal Sclerotherapy for Congenital Cystic Adenomatoid Malformation of the Lung; Fetal Diagn Ther 2008; 24:237-240). This minimally-invasive approach has essentially removed the indication for open fetal surgery for CCAM associated with hydrops.	We have added a sentence indicating that some cases have been treated with sclerotherapy and referenced the publication.
Peer Reviewer #13	Tables	University of Maryland and University of NC are a NAFTNet Affialiate Centers; You may want to confirm with UNC, if REX or the Hospital of UNC, Chapel Hill, is the affilate hospital.	Corrected.
Peer Reviewer #13	Tables	Columbia Unviersity, Phoneix Perinatal Associates, and Materanal Fetal Services of Utah are NAFTNet Affiliate Centers	Corrected.
Peer Reviewer #13	Tables	The program in Tampa has relocated to Miami. To the best of this reviewer's knowledge, there is no longer a program in Tampa	Corrected.
Peer Reviewer #13	Tables	Blue Cross Blue Shield: please confirm "TTTS (laser ablation): medically appropriate if diagnosis is made before "28" weeks gestation. Laser is rarely offered after 26 weeks. FDA guidelines for the only approve fetoscope, which is under a humaniatry exemption,	We have removed this information.

		limited the procedure to16-26 weeks.	
Public Reviewer #1	Tables	Cardiac study populations table 6- there are 20 studies mentioned not 10 as listed	Corrected.
Public Reviewer #2	Tables	Please note that it is not accurate to represent the information in Table 5 in the row labeled Blue Cross Blue Shield (BCBS) as Insurance Coverage for BCBS Plans. The information in the table appears to be based on Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) Assessments from 1998 and 1999. TEC Assessments are scientific opinions, provided solely for informational purposes. TEC Assessments should not be construed to suggest that TEC recommends, advocates or requires the payment or nonpayment of the technology or technologies evaluated. Each separately owned and operated Blue Cross and Blue Shield Plan (such as Regence Blue Cross and Blue Shield, also referred to in Table 5) makes its own coverage decisions. Blue Cross and Blue Shield Plans are free to use the Association's Assessments as an information source, but they are under no obligation to do so. Thus, it is incorrect to represent the information in Table 5 in the row labeled Blue Cross Blue Shield as Insurance Coverage.	We have removed this information and changed the table to note that it highlights "selected policies."
Public Reviewer #3	Tables	Please explain here or in discussion section about why the majority of centers listed in Table 3 are not NAFTnet members?	Corrected table.
Peer Reviewer #7	Appendices	This trial seems to refer to UCSF. In fact, there arecurrently two institutions that have open enrollment fortracheal occlusion for CDH. Both studies are conductedunder the auspices of the FDA, using an InvestigationalDevice Exemption: UCSF (IDE #G080053) and BrownFetal Program in Providence (IDE #G080077). Neitherstudy is currently funded, but	Thank you for this information.

		both institutions havesince applied for funding of a joined, two-institutionstudy with the FDA (Orphan Disease Grant). The study criteria are similar to what is described here – except for the exclusion criterion that "patient is unable to stay in San Francisco for the duration of the pregnancy." In fact, it is San Francisco or Providence, RI – and it is until removal of the plug at 34 weeks, not until the end of the pregnancy. Furthermore, the original UCSF study has lung growth as primary outcome and survival as secondary outcome, whereas the Brown study has survival as primary and lung growth as secondary; the joint proposal has survival as primary outcome and lung growth as secondary.	