Horizon Scanning in Surgery: Application to Surgical Education and Practice

Serial transverse enteroplasty (STEP) for patients with short bowel syndrome (SBS)

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Disclaimer

This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

This report is not intended to be used as medical advice or to diagnose, treat, cure or prevent any disease, nor should it be used for therapeutic purposes or as a substitute for a health professional's advice. The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) does not accept any liability for any injury, loss or damage incurred by use of or reliance on the information.

Objective

This horizon scanning assessment provides short, rapidly completed, 'state of play' documents. These provide current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

Introduction

Background

The small intestine, or small bowel, is approximately 6.5 meters long and 2.5 centimeters wide and consists of three continuous sections; the duodenum (first 20 to 25 centimeters), the jejunum (first two fifths after the duodenum), and the ileum (remaining three fifths). Food exits the stomach and passes through the duodenum, which continues the breakdown process by mixing pancreatic and bile secretions with the food. Further transit through the jejunum and ileum results in the absorption of nutrients and water. The subsequent waste continues its journey through the ileocecal valve into the colon, where much of the remaining fluid is absorbed and the waste can be stored ready for excretion.

Short bowel syndrome (SBS) is defined as a malabsorptive state that is associated with extensive resection of the small bowel as well as a range of congenital conditions. Significant reductions in bowel length result in inadequate functional mucosal surface area and a reduction in bowel transit time (Wales et al 2007). Depending on the severity of SBS, this can lead to dehydration secondary to diarrhea, malabsorption of macro- and micro- nutrients, malnutrition, and failure to thrive (Vanderhoof and Langnas 1997).

The syndrome affects both adults and infants, although the etiology often differs between the two patient populations (Vanderhoof and Langnas 1997):

- in adults, common causes of SBS are post-resection malignancy, radiation, Crohn's disease and vascular insufficiency
- in infants, necrotizing enterocolitis and intestinal anomalies are primarily responsible.

The small bowel naturally controls secretion of several gastric products via negative feedback mechanisms, i.e., inhibition of gastrin secretion and reduction in gastric acid production. These mechanisms are impaired following bowel resection, resulting in a higher incidence of peptic ulcer disease, gastroesophageal reflux disease and proximal small bowel inflammation (Vanderhoof and Langnas 1997). Symptoms are dependent on the characteristics of the remaining intestine.

Resection of the duodenum can result in poor iron, folate and/or calcium absorption, whereas resection of the ileum (primarily responsible for the reabsorption of secretions) can result in massive fluid loss. The jejunum generally adapts better to resection than the ileum. However, terminal resection of the jejunum can remove the ileocecal valve (which presents a barrier to reflux of colonic bacteria), resulting in a higher incidence of bacterial overgrowth in some cases.

SBS can be avoided after less extensive resections because the remaining small bowel adapts via lengthening of villi, increase in bowel absorptive surface area, and improved digestive and absorptive functions. Such adaptations can be aided through the administration of growth factors to promote enterocyte and/or colonocyte proliferation (Wilmore and Robinson 2000).

Post-operative management of SBS is a multistage process. Initially a patient requires administration of parenteral nutrition (PN; the intravenous provision of total nutrient requirements). Another important aspect of postoperative management involves monitoring and correcting large fluid and electrolyte losses (Vanderhoof and Langnas 1997). Following stabilization, the patient can slowly return to enteric (normal) feeding, usually based on an elemental diet using individual amino acids and/or di- and tri- peptides as a protein source. Complex diets can also be provided, and although harder to digest than elemental diets, these may be more effective in stimulating intestinal adaptation (Vanderhoof and Langnas 1997). As recovery progresses, parenteral feeding can be slowly reduced, with enteric feeding becoming the predominant method of nutritional support. Treatment of SBS may also include the administration of antidiarrheal medications, antisecretory agents and antimicrobials for treatment of patients with bacterial overgrowth (Shatnawei et al 2010).

Many patients do not possess the digestive capacity to extract sufficient nutrients from enteric diets, causing them to become permanently dependent on total parenteral nutrition (TPN) for some or all of their caloric requirements. Unfortunately, several chronic complications are associated with parenteral feeding, including TPN-induced liver disease, recurrent catheter sepsis, small bowel bacterial overgrowth and nutrient deficiency (Vanderhoof and Langnas 1997). Continued complications and further advancement of nutrient deficiencies may result in the need for enteroplasty or intestinal transplantation.

Burden of disease

Disease incidence

To date no accurate SBS incidence and mortality estimates have been published due to the rarity of the syndrome, conflicting definitions of SBS among institutions, follow-up problems, and problems defining catchment populations (Wales et al 2004).

In infants, SBS is more common in premature newborns due to congenital abnormalities and the increased risk of necrotizing enterocolitis. Two studies have attempted to quantify the incidence of SBS in pediatric populations. In a study published by Wales et al (2004), estimates were based on admissions to the Hospital for Sick Children (HSC) in Toronto (Canada). The second study (Cole et al 2008) pooled data from 16 tertiary centers in the United States (US) and suggested an SBS incidence less than half that of Wales et al (2004; see Table 1) although in this study only surgical SBS cases were included, and diagnosis was limited to infants who underwent significant resection of the bowel resulting in PN dependence (Cole et al 2008).

Table 1: Estimates at incidence of SBS in pediatric populations.

Study	Year	Location	Rate per 1000 admissions	Incidence per 100,000 live births	Comment on Study
Wales et al	2004	Canada	Full-term, 3.1	Full-term, 3.5	Comparison of SBS incidence between full term and premature neonates
			Premature, 43.6	Premature, 353.7	
			Overall, 22.1	Overall, 24.5	
Cole et al	2008	US	VLBW, 7 (0.7%)	Not reported	Surgical SBS
			ELBW, 11 (1.1%)		

VLBW: very low birth weight; ELBW: extremely low birth weight; SBS: short bowel syndrome

Quality of life (QOL)

Quality of life for a patient with SBS can be greatly diminished, particularly for those who are dependent on PN for their primary source of sustenance. Dependence on home parenteral nutrition (HPN) can lead to significant psychological symptoms and sexual and social dysfunction, with most patients unable to return to work (Carlsson et al 2003). One study used short form (SF) -36[1] and health-related quality of life (HRQOL) questionnaires to assess perceived QOL for 28 patients (Carlsson et al 2003). Results demonstrate a marked reduction in every QOL variable measured as compared to controls, and a further reduction in QOL for patients with SBS who required HPN (Carlsson et al 2003).

[1] The SF-36 is a multi-purpose, short-form health survey of 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. See http://www.sf-36.org/ for more information.

Technology

Serial transverse enteroplasty (STEP)

STEP is similar to its main comparator, longitudinal intestinal lengthening and tapering (LILT, or the Bianchi procedure) in that it increases the length of the small bowel by extending the pre-existing tissue. Initially, the bowel is flattened and a line is drawn along the antimesenteric border to maintain orientation during surgery. A catheter is passed through a small incision, providing a guide through which to pass the larger side of an endoscopic gastrointestinal anastomosis (GIA) stapler (Kim et al 2003). Application of the stapler perpendicular to the long axis of the bowel from alternating sides creates a zig-zag pattern, generating a channel width of approximately 2 centimeters (see Figure 1). The zig-zag pattern flattens out several weeks after surgery, with the staple lines being the only evidence of extension (Jones et al 2010).

Following STEP, dilatation of the small bowel can allow one or more additional STEP procedures ("re-STEP"). This procedure can also be used to further extend small bowels that had previously undergone LILT extension, as was the case for the first human STEP procedure (Kim et al 2003). Although STEP presents a viable replacement surgery for LILT, Kim et al (2003) suggest that, assuming the bowel is dilated sufficiently, a LILT procedure should be the first option, with the STEP procedure best used as a subsequent procedure. (Note that STEP can be performed on a small bowel previously lengthened by LILT, but not the reverse.)

Unlike LILT, the STEP procedure can be performed on patients with a foreshortened mesentery and/or loss of vascularity in one leaf of the mesentery (Sudan et al 2007). In comparison to LILT, STEP is technically less difficult, presents a decreased risk of intestinal ischemia as it preserves the natural vascular anatomy of the bowel, and results in a decreased risk of intraperitoneal contamination as the bowel is never opened (Modi et al 2006).

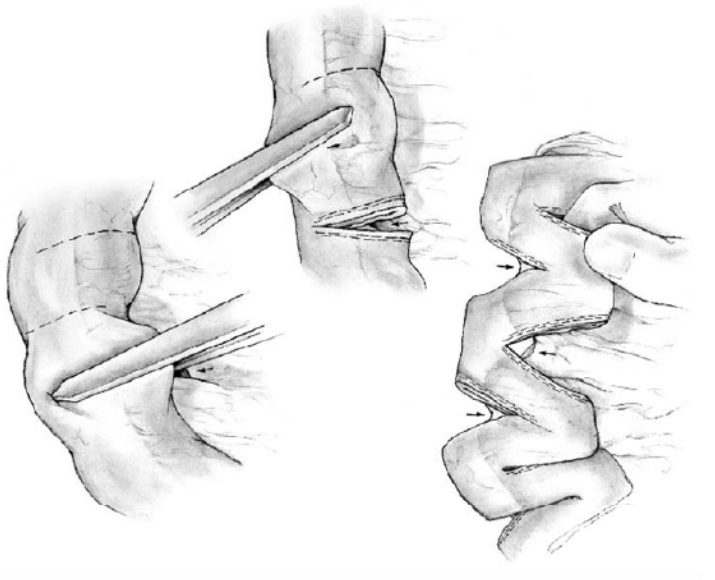

Figure 1: The STEP procedure (*adapted from Jones et al 2010*)

Stage of development

The STEP procedure was developed and employed on the first human patient in 2003 (Kim et al 2003). Since its inception, STEP appears to have been used in over 20 medical centers. The majority are located in the US; however, institutions based in Portugal, Spain, Poland and Canada have also performed STEP surgery. The main centers with respect to patient numbers and number of publications are in the US, i.e., the Children's Hospital Boston (at which the procedure was developed and first implemented) and the University of Nebraska Medical Center. At the date of report preparation, the STEP procedure had been in use for seven years, although long-term data are not readily available.

Regulatory approval

The first GIA stapler, used to perform the STEP procedure, was approved by the US Food and Drug Administration (FDA) in 1980 (*510k no: K801590*) and there are currently 11 such staplers approved for use in the US, the majority of which are improvements to previous staplers (Table 2).

Table 2: FDA-approved stapling devices utilized by the STEP procedure.

Name of device	Manufacturer	FDA approval number	FDA approval date
Autosuture endo GIA staplers with endo GIA single use loading units	Covidien LP, a division of Tyco Healthcare Group LP	K083519	04/10/2009
Auto suture endo GIA staplers with endo GIA single use loading units with staple line reinforcement	Tyco Healthcare Group LP	K080898	05/05/2008
Reprocessed autosuture GIA endoscopic staplers	Sterilmed, Inc.	K070930	10/18/2007
Auto suture endo GIA staplers	United States Surgical, A division of Tyco Healthcare	K061095	05/31/2006
Auto suture endoscopic (& open) GIA surgical stapling instrument	United States Surgical, a division of Tyco Healthcare	K032696	12/01/2003
Auto suture® powered endoscopic GIA™ stapler	United States Surgical, a division of Tyco Healthcare	K913802	10/17/1991
Auto suture® thin tissue GIA™ surgical stapler	United States Surgical, a division of Tyco Healthcare	K913211	09/25/1991
Modified auto suture endoscopic GIA surgical stapler	United States Surgical, a division of Tyco Healthcare	K900129	02/27/1990
Auto suture® endoscopic GIA™ surgical stapler	United States Surgical, a division of Tyco Healthcare	K892233	04/04/1989
Auto suture poly GIA surgical stapler	United States Surgical, a division of Tyco Healthcare	K843603	10/31/1984
Auto suture disposable GIA surgical stapler	United States Surgical, a division of Tyco Healthcare	K801590	08/04/1980

Current clinical trials

No clinical trials assessing the safety and efficacy of the STEP procedure appear to be underway (www.clinicaltrials.gov).

Current treatment and alternatives

Several surgical techniques can be employed to treat SBS, functionally resulting in:

- restoration of intestinal continuity: takedown enterostomy
- relief from obstruction and dysmotility: strictureplasty or bowel tapering for dilated bowel segments
- prolonged transit time: reversed intestinal segments, colonic interposition, or creation of artificial sphincters
- transplanted new intestine
- lengthening of the remaining dilated intestine: LILT or STEP.

The two most common alternatives to the STEP procedure are intestinal transplantation and LILT (Shatnawei et al 2010). Although a third lengthening and tapering surgical technique was developed, the Kimura and Soper technique (Kimura and Soper 1993), it is used infrequently and thus does not present an appropriate comparator to STEP.

Intestinal transplantation (ITx)

Patients who undergo massive resections (resulting in < 50 centimeters of remaining jejunum/ileum) often have severe nutritive deficiencies and complications. Some patients can be weaned off TPN following a bowel rehabilitation program; however, many require TPN for life and are candidates for intestinal transplantation (Wilmore & Robinson 2000).

Advances in patient care over the past decade have significantly increased the safety and efficacy of ITx in North America, with graft survival rates and patient survival rates increasing between 1997 and 2005 from 52% to 75% and 57% to 80%, respectively (Lennon 2010). Nearly 80% of post-transplant patients are successfully weaned from PN and resume the activities of daily life (Grant et al 2005).

Although ITx success rates are increasing, transplantation can result in significant technical and immunologic problems and is associated with high morbidity and mortality rates as well as costs, e.g., acute cellular rejection is experienced by 30% to 60% of transplant patients and graft loss resulting from chronic rejection affects more than 10% of children within the first 5 years after intestinal transplantation. The incidence of graft rejection has declined slightly due to the use of immunosuppressive drugs (Sindhi et al 2002); however, high-dose prophylactic immunosuppression often leads to lymphomas and as a result more than 10% of patients who undergo intestinal transplantation suffer from post-transplantation lymphoproliferative disorder (Sindhi et al 2002). In addition, there is a permanent risk of infectious diseases and secondary malignancies following intestinal transplantation, including myeloproliferative syndrome and de novo malignancies (Reinshagen et al 2008).

In an effort to reduce the use of immunosuppressive drugs without the increased risk of graft rejection, modifications to immunosuppressive regimes are currently being investigated, such as bone marrow-intestinal transplantation combinations (Wilmore & Robinson 2000) and the postoperative administration of immunosuppressive monoclonal antibodies such as alemtuzumab (Lennon 2010).

Longitudinal Intestinal Lengthening and Tailoring (LILT)

The LILT procedure was first described in 1980 and since then has been the predominant method employed to surgically lengthen the small bowel. The technique involves dividing the small bowel longitudinally using a surgical stapler, and then anastomizing the two sections together in an isoperistaltic fashion, effectively doubling the length of the dilated segment (see Figure 2) (Jones et al 2010). Although this procedure does not create any additional surface area for absorption, it has been demonstrated to increase the function of the small bowel.

There are currently no published systematic reviews or randomized controlled trials involving the LILT procedure. Statistical data (such as mortality, complications and reversion to intestinal transplantation rates) vary significantly among case series studies, making it difficult to draw evidence-based conclusions with regards to the safety and efficiency of LILT versus intestinal transplantation and STEP. For example, an institutional case series of 53 patients who were treated with the LILT procedure (Reinshagen et al 2008) resulted in a high survival rate, increased weight gain and a high quality of life among patients. In contrast, Walker et al (2006) demonstrated a low success rate among a cohort of 19 patients, with LILT being successful in only seven patients, and nine patients requiring intestinal transplantation at a mean of 4 years post-LILT.

The LILT procedure has several limitations: it is technically difficult, involves at least one intestinal anastomosis and places the mesenteric blood supply in jeopardy (Chang et al 2006). As mentioned previously, patients with a foreshortened mesentery and/or loss of vascularity in one leaf of the mesentery are not eligible (Sudan et al 2007). If the small bowel is still unable to function adequately following surgery, no further LILT procedures can be performed. However, follow up data suggest that LILT can be effective in the long term. Reinshagen et al (2008) analyzed outcomes for 53 LILT patients from their institution between 1987 and 2006, with mean follow up period of 80 months (range: 6-236 months). Data demonstrate a low level of mortality and PN dependence, and a high QOL scoring (Reinshagen et al 2008).

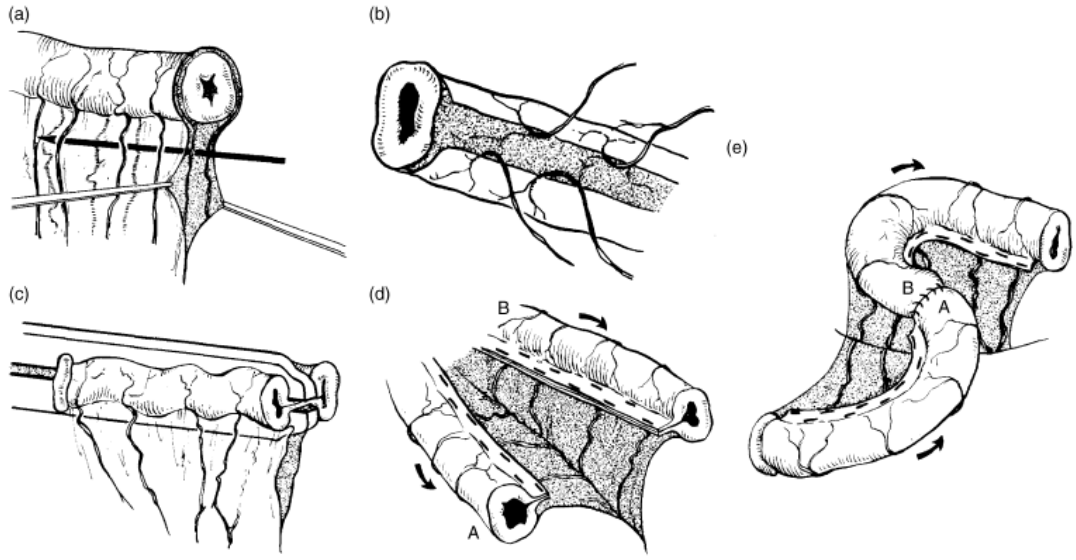

Figure 2: The LILT (Bianchi) Procedure (*adapted from Jones et al 2010*)

Literature review

Search criteria

Keyword/MeSH terms utilized:

Serial transverse enteroplasty, STEP, short bowel syndrome, intestinal lengthening

Databases utilized:
PubMed, OVID (EMBASE)

Inclusion criteria

Table 3: Inclusion criteria for identification of relevant studies.

Characteristic	Criteria
Publication type	Systematic literature reviews, randomized controlled trials, non-randomized comparative studies, case series
Patient	Patients with SBS
Intervention	STEP for small bowel lengthening
Comparator	LILT (Bianchi procedure)
Outcomes	Increased bowel length, reduced dependence on TPN, improved patient growth, avoidance of short bowel transplantation, improved intestinal motility, improved biomarkers of liver and digestive function
Language	English only

Included studies

Fourteen studies were identified for possible inclusion in this report with comparative studies being prioritized. Case series studies with fewer than 10 patients and case reports were then excluded. Ultimately five studies were eligible for inclusion (Table 4).

Table 4: Characteristics of included studies.

Level of evidence (Appendix B)	Study/location	Intervention and number of patients	Mean duration of follow-up
Level III-3 Comparative	Sudan et al 2007 United States	Group A (STEP procedure): 21 patients Group B (LILT procedure): 43 patients	STEP: 1.7 years LILT: 5.9 years
Level IV Case Series (ordered from largest patient enrollment)	Modi et al 2007* United States	STEP procedure: 38 patients	12.6 Months
	Ching et al 2009 United States	STEP procedure: 16 patients	23 Months
	Wales et al 2007 Canada	STEP procedure: 14 patients	23 Months
	Andres et al 2008 United States	Re-STEP procedure (secondary to primary STEP or LILT): 14 patients	14.5 months

*on behalf of the International STEP Data Registry
STEP: serial transverse enteroplasty; LILT: Longitudinal Intestinal Lengthening and Tailoring

Critical appraisal

Comparative evidence

One single retrospective comparative study was identified in our searches (Sudan et al 2007). Data presented from a single institution cohort of 64 patients detailed 77 lengthening procedures performed between 1982 and 2007. All patients underwent intestinal lengthening surgery using either the STEP procedure (n=21) or the LILT procedure (n=43). Fifty patients were pediatric (≤ 17 years) and 14 patients were adult (≥ 18 years). Differences in gender were apparent in both the STEP (7 female; 14 male) and LILT (25 female; 18 male) treatment groups. Complete figures with regards to the distribution of adult and pediatric patients between the two lengthening procedures were not reported.

Indications for surgical lengthening were twofold; each patient had dilated small bowel loops on endoscopy or radiologic imaging studies, as well as TPN dependence with poor enteral progression/adaptation. Two patients in the LILT group were not TPN-dependent; however, they were still included in the analysis of results. Furthermore, patients who were not eligible for the LILT procedure due to loss of vascularity in one leaf of the mesentery from prior surgery and/or a foreshortened mesentery were included in the STEP cohort by default.

Thirteen patients underwent 14 re-STEP procedures as a result of recurrent bowel dilation, having previously undergone STEP surgery (n=5) or LILT surgery (n=8). Prior to surgery, 50% of patients with liver biopsies demonstrated cirrhosis or extensive bridging fibrosis. Two patients in the total cohort had undergone previous end colostomies and of the 62 remaining patients, only 10 (16%) possessed an ileocecal valve.

Outcomes included bowel length increase, reduced dependence on TPN, patient survival, the number of patients requiring intestinal transplantation, intra- and post- operative complications, patient growth after lengthening and mortality. The authors also performed a statistical analysis of risk factors influencing: mortality, ability to wean from PN and requirement for transplantation. Patients undergoing STEP had a mean follow up time of 1.7 years, compared with a mean follow up time of 5.9 years for LILT patients (Sudan et al 2007).

Case series evidence

Four case series studies were included in this report. One may overlap with patients reported by Sudan et al (2007); however, as it provides outcomes specific to a select subgroup of patients (re-STEP patients) it remains eligible for inclusion (Andres et al 2008). Two further studies have undefined patient overlap, one being a single institution study with a cohort of 16 patients from the Children's Hospital Boston (Ching et al 2009) and the second a multiple institution registry of 38 patients (Modi et al 2007), which also included patients from the Children's Hospital Boston. Although the exact number of patients was not specified, Modi et al (2007) states that each institution included ≤ 10 patients in the STEP registry. The fourth study was a single institution study with a cohort of 14 patients (Wales et al 2007).

The first report from the International STEP Registry presents pooled data from 19 different institutions including 38 patients treated between September 2004 and April 2006 (Modi et al 2007). The focus is on pediatric patients. Primary diagnoses included intestinal atresia (n=13), gastroschisis with or without volvulus (n=11), necrotizing enterocolitis (n=7), malrotation with volvulus (n=2), segmental volvulus (n=2), Hirschsprung's disease (n=2) and congenital shortened bowel (n=1).

Data collected in this registry included gender and gestational age, primary diagnosis, comorbidities and surgical history. Operative data included pre- and post-operative intestinal

length and width, intraoperative complications and preoperative enteral tolerance. Postoperative data included late complications and changes in enteral tolerance. The mean follow-up period from STEP procedure to data analysis was 12.6 months (range: 0-66.9 months).

Patient median age was 1.3 years (range: 0-19.9 years), although this varied substantially based on clinical indications, i.e.,

- PN-dependent SBS (n=29; median age 1.2 years, range: 1 month – 19.9 years. *P < 0.05*)
- Bacterial overgrowth (n=6; median age 13.9 years, range: 2.0-19.6 years. *P < 0.05*)
- Neonatal atresia with marginal residual bowel length (n=3; median age 3 days, range: 0-4 days. *P < 0.05*).

Ching et al (2009) presented data from a retrospective review of STEP for 16 pediatric patients (2002 to 2008). Median patient age was 12 months (range: 1.5-65 months), and median follow up was 23 months (range: 1-71 months). Indications for surgery involved failure to advance enteral feedings (n=11), bacterial overgrowth (n=3) and neonatal atresia (n=2). Primary diagnoses included gastroschisis (n=6), intestinal atresia (n=4), midgut volvulus (n=3), necrotizing enterocolitis (n=2) and Hirschsprung's disease (n=1). Three patients had previously undergone lengthening surgery using the LILT procedure. Outcomes included change in bowel length and width, complications, weight-for-age scoring, improved enteral tolerance and transition off PN, and post-STEP transplantations.

Between May 2003 and May 2006, 14 patients underwent the STEP lengthening procedure at the Hospital for Sick Children (Toronto, Canada; Wales et al 2007). Indications included PN-associated cholestasis (n=6) and bacterial overgrowth (n=7), primarily as a result of jejunoileal atresia (n=7) and necrotizing enterocolitis (NEC, n=4). Other diagnoses were gastroschisis (n=1), Hirschsprung's disease (n=1) and volvulus (n=1). Two patients had received previous short bowel enteroplasty but required further intervention due to recurrent bowel dilatation. The mean follow-up period was 23 months (standard deviation SD: 9 months).Operative outcomes included bowel length increase, length of colon, number of linear stapler cartridges used, and stapler costs per operation. Clinical outcomes included weight gain, reduced dependence on PN, stool frequency and consistency, and tests of intestinal absorptive capacity (citrulline, D-xylose, alpha-1 AT concentrations and percentage of fecal fat).

Finally, Andres et al (2008) retrospectively reviewed data on 14 patients who had undergone a re-STEP procedure at their institution between May 2002 and October 2007. All patients were diagnosed with irreversible intestinal failure. Indications for surgery at this institution (University of Nebraska Medical Center) were described by Sudan et al 2007. Two patients underwent more than one re-STEP procedure, and a further two patients were adults who underwent LILT lengthening in childhood. Median time following original lengthening procedure was 12 months (range: 2 months – 15 years), and included 12 pediatric patients and 2 adult patients. Prior to re-STEP, seven patients had undergone LILT surgery and seven had undergone STEP surgery. Outcomes included analysis of liver function, nutritional characteristics, increased intestinal length, height and weight z scores, ability to wean from PN, mortality, and need for intestinal transplantation.

In summary, only one study compared STEP to another treatment option (the LILT procedure) and this retrospective review is of low quality. The majority of data for our report comes from case series studies which are historically more susceptible to bias. Furthermore, studies varied with regards to inclusion and exclusion criteria, primary diagnoses, and other variables such as patient

age and initial small bowel length, making generalizations difficult. More high quality comparative evidence is required in order to directly compare safety and efficacy outcomes between STEP and other treatment options.

Safety and efficacy

Safety

In general, a high number of complications developed following STEP surgery, although the majority of these were not major and consisted of repeat hospital admission to correct fluid imbalances and/or antibiotic administration to resolve infection.

The frequency of mortality was low in most studies (with the exception of Wales et al 2007), and occurred primarily as the result of liver failure and sepsis. The requirement for bowel transplantation post-STEP was also relatively low with the main indications being progressive liver disease, feeding intolerance and line sepsis (Table 5).

Table 5: Complications, mortality and requirement for intestinal transplantation following STEP.

Study	n	Complications	Mortality	Transplant (%)
Sudan et al (2007)	64	12/64 (11%)	6/64 (9%)	9/64 (14%)
STEP	21	NR	NR	1/21 (4.8%)
LILT	43	NR	NR	8/43 (18.6%)
Modi et al (2007)	38	9/38 (24%)*	3/38 (8%)	3/38 (8%)
Ching et al (2009)	16	8/16 (50%)**	0/16 (0%)	2/16 (13%)
Wales et al (2007)	14	3/14 (21%)	3/14 (21%)	2/14 (14%)
Andres et al (2008)	14	*See text*	0/14 (0%)	4/14 (29%)

*3 intraoperative complications, 6 postoperative complications.
**study does not provide data as to whether one patient experienced more than one complication, or if eight patients experienced one complication each.

Sudan et al (2007) reported 6 deaths in all 64 patients, although they did not separate deaths by procedure, or early versus late complications between the two groups, stating that there was no difference in survival based procedure. Seven of the twelve complications recorded were early major postoperative complications, including high-grade obstruction (n=3) after STEP lengthening, and anastomotic leak (n=1), intestinal obstruction (n=1), necrosis of 1 of the 2 loops of bowel due to vascular injury (n=1) and pneumonia (n=1) after LILT lengthening. Late complications included anastomotic stricture (n=2) and interloop fistulae (n=3), all occurring in patients who received the LILT procedure.

In addition to significant complications, it was noted that nearly all patients experienced one or more episodes of infection following surgery, and many more required hospitalization on more than one occasion to correct fluid and electrolyte imbalances and/or for administration of intravenous antibiotics. Nine patients required small bowel transplantation due to loss of venous access (n=2), jaundice (n=4) and recurrent line-related septicaemia (n=3). Of the six deaths, five occurred in children due to sepsis, and one occurred in an adult with liver failure and sepsis after refusing bowel transplantation.

Mortality was associated with failure to wean from TPN, patient age < 12 months, prolonged international normalized ratio at time of lengthening surgery, and extensive bridging fibrosis or cirrhosis. Failure to wean from TPN was associated with shorter bowel lengths following surgical lengthening and reduced enteric calories prior to surgery, demonstrating that those less

dependent on TPN prior to surgery and who achieved the greatest final bowel lengths had higher enteric nutrition tolerance. Finally, five primary factors were associated with an increase in the requirement for bowel transplantation including surgical procedure (LILT 19% versus STEP 5%; possibly due to shorter follow-up period for patients with STEP); shorter bowel remnant pre-surgery; final bowel length after surgery; presence of jaundice; and lower percentage of total calories via enteral nutrition at 3 months and 6 months post-surgery.

Modi et al (2007) (n=38) reported three intraoperative complications: staple line leak (n=2) and aspiration of gastric contents (n=1). Postoperative complications included bowel obstruction (n=2), hypertension (n=1), intra-abdominal hematoma (n=1), intra-abdominal abscess (n=1) and serous pleural effusion (n=1). Transplantation was required for five patients due to progressive liver failure (n=3) and continued feeding intolerance and progressive liver disease (n=2). Of these five patients, one underwent multivisceral transplantation and the other four underwent or were awaiting combined liver and intestine transplantation at the time of publication. Three additional patients were removed from the transplant list due to post-STEP improvements in enteral tolerance. Three deaths occurred, all due to progressive liver failure and sepsis.

Ching et al (2009) (n=16) reported no fatalities. Complications included catheter-related bacteremias (n=5), the need for redilatation (n=5), gastrointestinal bleeding (n=2), and small bowel obstruction (n=1). Two patients underwent post-STEP transplantation, one multivisceral and one combined liver.

Wales et al (2007) (n=16) reported three complications and three deaths:

- One patient experienced significant gastrointestinal hemorrhage 8 months post-STEP caused by ulcers within the lengthened segment, all of which were along the staple line. Postoperatively the patient improved and was weaned off PN at 15 months post-STEP; however, at 22 months post-STEP the patient developed repeat intestinal bleeding, which was yet to be resolved at the time of publication.
- Two patients experienced a leak along the staple line and underwent emergency laparotomy. The bowel healed in both cases; however, both patients ultimately died.
- The third death was due to line sepsis and subsequent hepatic failure 3 months post-STEP.

Andres et al (2008) noted significant complications in several patients, stating that 64% of patients required further surgery or hospital admission for medical complications following re-STEP. Late surgical complications were experienced by three patients, two as a result of strictures and one as a result of short bowel obstruction as a result of a floppy dilated duodenum. Six patients required multiple admissions due to line sepsis. Of these patients, four required transplantation while two were progressively weaned off PN.

Efficacy

In a report prepared by the National Institute for Health and Clinical Excellence (Interventional Procedures Programme, NICE, UK), the authors received feedback from specialists defining the key efficacy outcomes of the STEP procedure. These included increased bowel length, reduced

dependence on TPN, improved patient growth and intestinal motility, avoidance of intestinal transplantation and improved biomarkers of liver function. The majority of studies included in this report provide data on some or all of these efficacy outcomes.

Table 6: Short bowel length and width before and after STEP.

Study	Remnant bowel length (mean + range *or* SD)			Remnant bowel width (mean)	
	Before (cm)	**After (cm)**	**Δ%**	**Before (cm)**	**After (cm)**
Sudan et al (2007)					
STEP	45 (11-122)	65 (23-150)	52% (12-200)	7 (3-10)	Not reported
LILT	44 (14-150)	68 (20-160)	48% (7-83)	6.5 (3-12)	Not reported
P value	*0.74*	*0.57*	*0.01*	*Not reported*	*0.76*
Modi et al (2007)	68 ± 44	115 ± 87	69%	6.3 ± 3.9	2.1 ± 0.9
P value	*n=27, P < 0.0001*			*n=30, P < 0.0001*	
Ching et al (2009)	60 (30-108)	117 (62-209)	91 ± 38%	6.5 (4.5-8.0)	2.0 (1.0-2.6)
Wales et al (2007)	107 ± 48	146 ± 58	49 ± 42%	6 ± 1	2 ± 0
Andres et al (2008)	56.5 (27-100)	90 (39-120)	Not reported	Not reported	Not reported

SD: standard deviation; Δ%: change in short bowel length expressed as a percentage

The majority of studies achieved significant lengthening of the bowel following the STEP procedure (mean range 49% to 91%; Table 6). Only marginal differences were observed in small bowel length increases between the STEP and LILT cohorts of patients in Sudan et al (2007), although it was noted that only the STEP procedure was capable of increasing bowel length by more than 100% (STEP and LILT maximum ranges plateaued at 200% and 83%, respectively). Bowel width was reduced roughly three-fold in each of the studies, from about 6 centimeter to 2 centimeter.

All patients who suffer from SBS have some requirement for PN, many having total dependence. Sudan et al (2007) (n=38) provides total figures for PN dependence, but does not separate these figures between the STEP and LILT groups of patients (Table 7). Patients who died (n=3), underwent intestinal transplantation (n=3), and neonates (n=3) were excluded from PN-dependent classification in Modi et al (2007), reducing the cohort to 29 patients, of which 21 were PN dependent prior to surgery. Of the four studies that provide data on PN dependence, only Andres et al (2008) demonstrates a less than 50% reduction in patients dependent on PN although patients in this study had undergone secondary lengthening procedures.

Table 7: Percentage of patients dependent on parenteral nutrition before and after STEP, and total calories provided through enteral nutrition.

	PN dependence (n, %)		Total enteric calories (%)		Post-STEP time
Study	**Before**	**After**	**Before**	**After**	
Sudan et al	62/64	29/62 (42%)	-	-	

(2007)	(97%)				
STEP	Not reported	40%	10 (30-100)	93 (25-100)	6 months
LILT	Not reported	45%	18 (0-100)	70 (0-100)	6 months
P value	*Not reported*	*Not reported*	*0.84*	*0.26*	
Modi et al (2007)	21/29 (72%)	11/29 (38%)	31 ± 31*	67 ± 37*	12.6 months (0-66.9 months)
P value			*n=21, P < 0.01*		
Ching et al (2009)	11/16 (69%)	5/16 (31%)		+1.4% per month	Median 23 months (1-71 months)
Wales et al (2007)	NR	1/8**	71 ± 21*	12 ± 24*	≥ 12 months
Andres et al (2008)	14/14 (100%)	8/14 (57%)	Child: 33 (0-68) Adult: 50 (40-60)	Not reported	Median 3 months (0.5-13 months)

*Expressed as percentage of total parenteral calories (reverse of enteric calories) at pre-STEP and 12 months post-STEP

**Seven of eight patients followed more than 1 year have weaned from PN.

All studies recorded increases in enteric calorie tolerance following surgery of at least 100%, with the exception of Ching et al (2009) where a mean increase of 1.4% per month for 30 months was reported, suggesting a total mean enteric calorie increase of 42%. For both PN dependence and percentage of enteric calories tolerated, accurate comparisons among studies are difficult due to the different timeframes used. For example, a greater percentage of patients were still dependent on PN at the time of follow up in the Andres et al (2008) study compared to the Ching et al (2009) study but median follow-up in the former was only 3 months versus 23 months for the latter.

Three studies assessed patient growth before and after STEP lengthening using height median z scores and weight median z scores. In the study by Sudan et al (2007), pre-operative height z scores and weight z scores were measured for patients receiving STEP (-1.97; range:-7.52 – 0.5; and -1.15; range: -7.29 – 0.5, respectively) and LILT (-1.89; range: -5.98 – 0.43; and -1.36; range: -3.46 – 0.62, respectively). Although post-surgery figures are not presented, the authors graphically demonstrate a correlation between growth and ability to wean from PN following surgery, with increased median z scores (improved growth) following surgery for those patients who were weaned from PN and reduced median z scores (reduced growth) in those patients who were unable to wean. In the study by Ching et al (2009), no initial height and weight z scores were provided, although post-STEP data showed a mean increase in weight-for-age z scores of 0.03 units/month ($P = 0.0001$), height-for-age z scores of 0.02 units/month ($P = 0.004$), and weight-for-height z scores of 0.04 units/month ($P = 0.02$) following surgery. A significant improvement in weight and height z scores was observed in patients who underwent re-STEP procedures (Andres et al 2010).

One study measured liver biomarkers at three time points; pre-intestinal lengthening surgery, pre-reSTEP and post-reSTEP (Andres et al 2010), with Sudan et al (2007) providing equivalent data for pre-STEP patients only. Patients in the re-STEP cohort underwent a stepwise

improvement in biomarker levels, with initial improvements following original intestinal lengthening, and further improvements following re-STEP (Table 8).

Table 8: change in levels of liver biomarkers before initial lengthening surgery, before reSTEP, and after reSTEP.

	Initial	pre-reSTEP	post-reSTEP	*P value*
Total Bilirubin (mg/dL)	1.1 (0.1–13.7)	0.6 (0.1-6.3)	0.2 (0.1-1.4)	*0.54*
Serum Albumin (mg/dL)	3.0 (2.5-3.6)	3.1 (2.6-4.3)	3.9 (3.2-4.6)	*0.03*
Platelet count (/mm3)	275 (145-531)	272 (42-448)	255 (124-440)	*0.28*
INR	1.2 (1-1.4)	1.2 (1-1.4)	1.2 1-1.4)	*0.61*

INR: international normalized ratio. All values are presented as mean (range).

One study provided pre- and post-STEP levels of digestive biomarkers (Wales et al 2007). Concentrations of citrulline and D-xylose both increased 12 months post-STEP (17 umol/L ± SD 9 to 33 umol/L ± SD 7 ($P < 0.05$); and 0.82 umol/L ± SD 0.39 to 2.13 umol/L ± SD 1.34, respectively), whereas Alpha-1 AT and fecal fat both decreased in the same time period (26 mL/d ± SD 8 to 15 mL/d ± SD 12; and 43% ± SD 24 to 23% ± SD 12, respectively). In addition, although an increase in intestinal length was observed in each case, transit time decreased from 155 ± 140 minutes to 121 ± 105 minutes following the STEP procedure.

Cost impact

No specific figures were available with regards to the total cost of the STEP procedure or its main comparator, LILT. In the study published by Wales et al (2007), the author suggests that the mean number of linear stapler firings was 16 (SD 9), resulting in a mean stapler cost of $2878.51 (SD $1406.22) (2006 Canadian dollars).

One of the primary indications for the STEP procedure is a dependence on TPN, and as such a reduction or elimination of TPN is one of the main measures of surgical success. Schalamon et al (2003) estimated the costs associated with TPN in-hospital and HPN to be USD$205,000 and USD$90,000 per year, respectively. Marshall et al (2005) derived similar figures for TPN in-hospital (Can$207,000 ± SD $54,000 per year) but presented much higher figures for HPN (Can$148,000 ± SD $47,000 per year). Costs include procedures, hospitalization, parenteral nutrition solutions, medical equipment and laboratory testing for in-hospital TPN; and costs of daily care (nutrition-support nurse, disposable supplies, nutrition solution) and follow up referrals (hospital and laboratory testing) for HPN.

Abu-Elmagd et al (1999) presented a transplantation cost analysis: USD$132,285 for intestinal transplantation, USD$214,716 for combined liver-intestine transplantation, and USD$219,098 for multivisceral transplantation. The authors concluded that transplantation becomes a cost-effective alternative to PN by the second year after transplantation; however, the costs of subsequent immunosuppressive drug regimes and costs associated with transplantation rejection and/or treatment of lymphomas and other secondary malignancies are not taken into account.

STEP could be cost saving when it results in a reduced requirement or elimination of TPN and avoidance of transplantation; however, without comparative cost data it is unknown as to whether STEP would be more economically feasible than LILT.

Clinical practice guidelines and consensus statements

There have been no clinical practice guidelines developed through which to base recommendations and advice relating to the use of the STEP procedure.

Training and education impact

The panel of specialist advisers who provided opinion on the STEP procedural overview (Interventional Procedures Programme, NICE, UK) stated that the procedure was not technically difficult but advised apprenticeship or observance of an experienced surgeon prior to attempting the procedure. Although innovative, STEP uses existing technology and does not require the surgeon to learn new skills associated with novel devices, instead requiring an adaptation of existing surgical knowledge.

Summary

Regardless of etiology, SBS results in a patient's inability to extract sufficient nutrients from enteric feeding. Many patients subsequently require TPN which is extremely inconvenient, costly and can lead to significant liver damage. Such patients are candidates for either bowel transplantation or bowel lengthening using either the LILT or STEP procedure.

The safety and effectiveness of bowel transplantation has improved markedly over the past decade; however, significant problems are still common due to the need for immunosuppressive drugs. LILT has been proven effective over the long term; however, the procedure is technically demanding, cannot be performed on patients with mesenteric defects, and cannot be repeated on previously lengthened bowels.

STEP was developed in 2003 and presents an adjunct to and potential replacement for LILT. The procedure is less technically demanding than LILT, can be performed on intestinal segments already lengthened by LILT or STEP, and reduces complications associated with LILT such as intestinal ischemia and intraperitoneal contamination.

At present STEP is used as a final treatment for patients who have stopped progressing in enteral feeding and are dependent on TPN, although for many patients the application of STEP occurs too late when the patient has already developed TPN-derived liver disease. It has been suggested that such patients are poor candidates for lengthening and should be referred for combined liver-bowel transplantation instead (Sudan et al 2007).

STEP is associated with a low mortality rate and a moderate need for transplantation, although the majority of these transplantation procedures have occurred as a result of liver failure and could potentially have been avoided if intestinal lengthening surgery had occurred earlier (Sudan et al 2007). More than half of the patients in STEP studies were able to wean from PN nutrition and greatly increase enteric calorie tolerance, and these developments were associated with improved height and weight z scores post-STEP. Improved liver and digestive biomarkers were observed post-STEP; however, only a single study measured levels of each and further evidence is required. Although initial results suggest that STEP is as safe and effective as LILT, patient numbers are still relatively small and follow-up periods are too short to properly ascertain the durability of the procedure.

Recommendation

Evidence suggests that STEP represents a safe and effective means of surgical intestinal lengthening, primarily for those patients with SBS who either require intestinal lengthening yet do not fulfil the requirements for LILT, or as a tool to further lengthen the small bowel in patients who have previously undergone LILT or STEP procedure(s). Although STEP has the potential to replace LILT as the primary method of surgical lengthening, more data are required to ensure that the procedure is safe and effective in the long term.

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Appendix A

Additional papers not included in this assessment

Article reference	N=	Conclusions	Reason for exclusion
Cowles RA, Lobritto SJ, Stylianos S, Brodie S, Smith LJ, Jan D. Serial transverse enteroplasty in a newborn patient. *Journal of Pediatric Gastroenterology and Nutrition* 2007;45(2):257-60	1	Feasible in the newborn patient	Case report
Morikawa N, Kuroda T, Kitano Y, Tanaka H, Takayasu H, Fujino A, Shibata Y, Tanemura H, Muto M, Honna T. Repeat STEP procedure to establish enteral nutrition in an infant with short bowel syndrome. *Pediatric Surgery International* 2009;25(11):1007-11	1	Safe and effective	Case report
Bogue CO, Alzahrani AI, Wales PW, John PR, Amaral JG. Delayed, life-threatening lower gastrointestinal hemorrhage in an infant after serial transverse enteroplasty: treatment with transcatheter n-butyl-2-cyanoacrylate embolization. *Pediatric Radiology* 2009;39(10):1098-101	1	Post-STEP complication; gastrointestinal hemorrhage	Case report
Ehrlich PF, Mychaliska GB, Teitelbaum DH. The 2 STEP: an approach to repeating a serial transverse enteroplasty. *Journal of Pediatric Surgery* 2007;42(5):819-22	2	Re-STEP is viable but needs to be performed with care	Case reports
Modi BP, Langer M, Duggan C, Kim HB, Jaksic T. Serial transverse enteroplasty for management of refractory D-lactic acidosis in short-bowel syndrome. *Journal of Pediatric Gastroenterology and Nutrition* 2006;43(3)395-7	1	Viable option for patients with refractory D-lactic acidosis	Case report
Duggan C, Piper H, Javid PJ, Valim C, Collier S, Kim HB, Jaksic T. Growth and nutritional status in infants with short-bowel syndrome after the serial transverse enteroplasty procedure. *Clinical Gastroenterology and Hepatology.* 2006;4(10):1237-41	4	STEP results in improved growth in the first year after surgery	Case reports
Kim HB, Lee PW, Garza J, Duggan C, Fauza D, Jaksic T. Serial transverse enteroplasty for short bowel syndrome: a case report. *Journal of Pediatric Surgery* 2003;38(6):881-5	1	Viable option for children with SBS	Case report

Studies excluded from this assessment

Yannam GR, Sudan DL, Grant W, Botha J, Langnas A, Thompson JS. Intestinal Lengthening in Adult Patients with Short Bowel Syndrome. *Journal of Gastrointestinal Surgery* 2010;Aug 24 [Epub ahead of print]	Duplicate patients (Sudan et al 2007) STEP procedures could not be separated from mixed data
Javid PJ, Kim HB, Duggan CP, Jaksic T. Serial transverse enteroplasty is associated with successful short-term outcomes in infants with short bowel syndrome. *Journal of Pediatric Surgery* 2005;40(6):1019-23	Duplicate patients (study) Small cohort (n=5)

Appendix B

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,5 among consecutive persons with a defined clinical presentation6	A prospective cohort study[7]	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation6	All or none[8]	All or none[8]	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilized.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6 Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

8 All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C with statistical adjustment for B).

10 Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).

11 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.