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Physiological track-and-trigger/early warning systems for use in maternity care (Review)

Smith V, Kenny LC, Sandall J, Devane D, Noonan M

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TABLE OF CONTENTS

[Intervention Review]

Physiological track-and-trigger/early warning systems for use in maternity care

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ABSTRACT

Background

A considerable challenge for maternity care providers is recognising clinical deterioration early in pregnant women. Professional bodies recommend the use of clinical assessment protocols or evaluation tools, commonly referred to as physiological track-and-trigger systems (TTS) or early warning systems (EWS), as a means of helping maternity care providers recognise actual or potential clinical deterioration early. TTS/EWS are clinician-administered (midwife, obstetrician), bedside physiological assessment protocols, charts or tools designed to record routinely assessed clinical parameters; that is, blood pressure, temperature, heart rate, urine output and mental/neurological alertness. In general, these systems involve the application of scores or alert indicators to the observed physiological parameters based on their prespecified limits of normality. The overall system score or alert limit is then used to assist the maternity care provider identify a need to escalate care. This, in turn, may allow for earlier intervention(s) to alter the course of the emerging critical illness and ultimately reduce or avoid mortality and morbidity sequelae.

Objectives

To evaluate the clinical- and cost-effectiveness of maternal physiological TTS/EWS on pregnancy, labour and birth, postpartum (up to 42 days) and neonatal outcomes.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register (28 May 2021), ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (7 June 2021), OpenGrey, the ProQuest Dissertations and Theses database (7 June 2021), and reference lists of retrieved studies.

Selection criteria

We included randomised and quasi-randomised controlled trials (RCTs), including cluster-RCTs, comparing physiological TTS/EWS with no system or another system. Participants were women who were pregnant or had given birth within the previous 42 days, at high risk and low risk for pregnancy, labour and birth, and postpartum complications.

Data collection and analysis

Two review authors (VS and MN) independently assessed all identified papers for inclusion and performed risk of bias assessments. Any discrepancies were resolved through discussion and consensus. Data extraction was also conducted independently by two review authors

(VS and MN) and checked for accuracy. We used the summary odds ratio (OR) with 95% confidence intervals (CIs) to present the results for dichotomous data and the mean difference (MD) with 95% CI to present the results for continuous data.

Main results

We included two studies, a parallel RCT involving 700 women and a stepped-wedge cluster trial involving 536,233 women. Both studies were published in 2019, and both were conducted in low-resource settings. The interventions were the 'Saving Mothers Score' (SMS) and the CRADLE Vital Sign Alert (VSA) device, and both interventions were compared with standard care. Both studies had low or unclear risk of bias on all seven risk of bias criteria. Evidence certainty, assessed using GRADE, ranged from very low to moderate certainty, mainly due to other bias as well as inconsistency and imprecision.

For women randomised to TTS/EWS compared to standard care there is probably little to no difference in maternal death (OR 0.80, 95% CI 0.30 to 2.11; 1 study, 536,233 participants; moderate-certainty evidence). Use of TTS/EWS compared to standard care may reduce total haemorrhage (OR 0.36, 95% CI 0.19 to 0.69; 1 study, 700 participants; low-certainty evidence). For women randomised to TTS/EWS compared to standard care there may be little to no difference in sepsis (OR 0.21, 95% CI 0.02 to 1.80; 1 study, 700 participants; low-certainty evidence), eclampsia (OR 1.50, 95% CI 0.74 to 3.03; 2 studies, 536,933 participants; low-certainty evidence) and HELLP (OR 0.21, 95% CI 0.01 to 4.40; 1 study, 700 participants; very low-certainty evidence), and probably little to no difference in maternal admission to the intensive care unit (ICU) (OR 0.78, 95% CI 0.53 to 1.15; 2 studies, 536,933 participants; moderate-certainty evidence). Use of TTS/EWS compared to standard care may reduce a woman's length of hospital stay (MD -1.21, 95% CI -1.78 to -0.64; 1 study, 700 participants; low-certainty evidence) but may result in little to no difference in neonatal death (OR 1.06, 95% CI 0.62 to 1.84; 1 study, 700 participants; low-certainty evidence). Cost-effectiveness measures were not measured in either of the two studies.

Authors' conclusions

Use of TTS/EWS in maternity care may be helpful in reducing some maternal outcomes such as haemorrhage and maternal length of hospital stay, possibly through early identification of clinical deterioration and escalation of care. The evidence suggests that the use of TTS/EWS compared to standard care probably results in little to no difference in maternal death and may result in little to no difference in neonatal death. Both of the included studies were conducted in low-resource settings where the use of TTS/EWS might potentially confer a different effect to TTS/EWS use in high-resource settings. Further high-quality trials in high- and middle-resource settings, as well as in discrete populations of high- and low-risk women, are required.

PLAIN LANGUAGE SUMMARY

Physiological track-and-trigger/early warning systems for use in maternity care

What is the question?

The aim of this review is to find out from randomised controlled trials if using simple monitoring tools are helpful in alerting to clinical problems and in reducing serious illness or death in pregnant women and in their first six weeks after birth. Examples of such tools are track and trigger systems or early warning systems kept by the bedside in maternity care.

Why is this important?

Many natural functional changes occur in a woman's body during pregnancy. As a result, a pregnant woman, who may appear healthy and well, can become rapidly very sick. This is called clinical deterioration. If not detected sufficiently early and treated successfully, the pregnant woman can become seriously ill or even die. Examples are serious bleeding, development of convulsions when a woman has high blood pressure, blood clots and serious infection. Simple bedside tools or charts can be used by maternity care providers (midwives and doctors) to record information on a woman's health. The recorded health measures include her blood pressure, pulse rate, breathing rate, body temperature, and other health measures such as urine output and mental alertness. The tools have been introduced so that the measures are observed, recorded and interpreted together, rather than as single measures. The intention is to detect when serious illness is, or might be developing. Medical staff can then step in to prevent serious harm.

What evidence did we find?

We searched for evidence on 28 May 2021 and identified two studies that compared an early warning system with standard care. One study was a single-centre study involving 700 women and the second was a stepped-wedge cluster trial (multiple centres grouped into 'clusters') involving 536,233 women. Different clusters of centres introduced the tool over time until all centres were using the tool. Both studies were carried out in low-resource healthcare settings. The tools were called the 'Saving Mothers Score' (SMS) and the CRADLE Vital Sign Alert (VSA) device. Risk of bias in the two studies was low or unclear.

We found that the tools probably do not reduce maternal death. Women may have less serious bleeding (or haemorrhage) when an early warning tool is used. This finding was supported by low-certainty evidence. We also found that the tools may make little or no difference to a potentially life-threatening body response to infection (sepsis), to blood pressure with swelling, protein in the urine and convulsions (eclampsia), to a serious illness in pregnancy that affects the blood and the way the liver works (HELLP), or being admitted to an intensive care unit (ICU). Use of the tools probably reduces the time a woman stays in hospital (moderate-certainty evidence). We also found that the

tools may make little or no difference to the death of the baby in the first month after birth (neonatal death). This finding was supported by low-certainty evidence. Neither of the two included studies reported cost outcomes.

What does this mean?

Use of early warning tools for women in maternity care in low-resource settings may reduce serious bleeding and probably reduces the number of days a woman stays in the hospital but may not reduce maternal or infant deaths. More studies are required on the different early warning systems in low-resource settings. Studies are also needed in middle- and high-resource settings, and in high- and low-risk pregnant women.

Summary of findings 1. TTS/EWS compared to standard care in maternity care

TTS/EWS compared to standard care in maternity care

Patient or population: maternity care
Setting: low-resource
Intervention: TTS/EWS
Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	Risk with TTS/EWS				
Maternal death	Study population		OR 0.80 (0.30 to 2.11)	536,233 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	
	0 per 1000	0 per 1000 (0 to 0)				
Haemorrhage	Study population		OR 0.36 (0.19 to 0.69)	700 (1 RCT)	⊕⊕⊖⊖ Low[b,c]	
	508 per 1000	271 per 1000 (164 to 416)				
Sepsis	Study population		OR 0.21 (0.02 to 1.80)	700 (1 RCT)	⊕⊕⊖⊖ Low[b,c]	
	242 per 1000	63 per 1000 (6 to 365)				
Eclampsia	Study population		OR 1.50 (0.74 to 3.03)	536,933 (2 RCTs)	⊕⊕⊖⊖ Low[a,b,d]	
	5 per 1000	8 per 1000 (4 to 16)				
HELLP count	Study population		OR 0.21 (0.01 to 4.40)	700 (1 RCT)	⊕⊖⊖⊖ Very low[a,c]	
	6 per 1000	1 per 1000 (0 to 24)				
Maternal admission to ICU	Study population		OR 0.78 (0.53 to 1.15)	536,933 (2 RCTs)	⊕⊕⊕⊖ Moderate[a,b]	
	1 per 1000	1 per 1000				

		(1 to 2)			
Perinatal death[$]	Study population		OR 1.06 (0.62 to 1.84)	700 (1 RCT)	⊕⊕⊖⊖ Low[b,c]
(neonatal death only; all women)	222 per 1000	232 per 1000 (150 to 345)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

[$] Perinatal death was not reported in either of the two included studies; data for neonatal death in all women (1 study) presented as a proxy measure of perinatal death in this Table.

CI: confidence interval; **HELLP**: haemolysis, elevated liver enzymes and low-platelet; **ICU**: intensive care unit; **OR**: odds ratio; **RCT**: randomised controlled trial; **TTS/EWS**: track-and-trigger systems/early warning systems

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] In the Vousden 2019 study, in the community settings of some clusters, the trial's outcomes might not have been documented previously. Use of the CRADLE VSA device might thus have resulted in increased reporting of the primary outcome during the intervention phase of the trial with a bias towards the intervention; thus we downgraded by 1 to serious for possible other bias.

[b] Although the study contributing to this outcome had low or unclear risk of bias for all risk of bias criteria, we downgraded by [a] to serious because of other bias. The authors state that it is possible that the direct involvement of the anaesthesiologist as the principal investigator might have enhanced the care in the group where the SMS chart was applied.

[c] Study sample size relatively small, based on prevalence of hypertensive disorders at the study site; wide 95% CI with very few events; we downgraded by 2 to very serious on possible imprecision.

[d] Point estimates vary somewhat across the studies; Chakravarthy 2019 data favours intervention and the Vousden 2019 data favours the control. We thus downgraded by 1 to serious for possible inconsistency.

BACKGROUND

A considerable challenge for maternity care providers is recognising clinical deterioration in pregnant women. Early recognition of disease is compromised by the physiological adaptation of healthy pregnancy which results in: i) an increased susceptibility to rapid disease progression (for example, sepsis secondary to the immunosuppression of normal pregnancy and haemorrhage secondary to a rapid increase in blood flow to the genital tract); and ii) altered clinical parameters and reference ranges compared to non-pregnant women (Carle 2013). Consequently, women may deteriorate rapidly from being apparently well to being critically sick and this is further compounded by the fact that standard clinical parameters do not apply. Together, these features increase the risk of maternal mortality or serious maternal morbidity (NCEC/HSE 2014).

Recently, professional bodies and guideline developers have been recommending the use of clinical assessment protocols or evaluation tools (ACOG 2011; RCOG 2011; RCOG 2012; DOH 2019; Knight 2019), commonly referred to as physiological track-and-trigger systems (TTS) or early warning systems (EWS), as a means of assisting maternity care providers with physiological assessment. The concept is that a compromised pregnant or postpartum woman can be identified early in the course of possible deterioration based on routine observation and assessment of the physiological parameters, standardised for pregnancy and indicative of well-being, that is, respiration rate, blood pressure, heart rate, etc. Early recognition enables early intervention with the ultimate intention that maternal and infant adverse outcomes are reduced or avoided (CMACE 2011; Maguire 2015).

Description of the condition

A well-established characteristic of critical illness in maternity care is that a pregnant woman, so far fit and well, can deteriorate rapidly from clinical conditions that result in maternal mortality or near-miss mortality and significant maternal morbidity events (e.g. ante- or postpartum haemorrhage, eclampsia, sepsis or thromboembolic disease, and their potential sequelae). Prior to the occurrence of such events, there may be a brief warning period when altered physiological parameters may be clinically observable and indicative of deterioration, for example, increased respiration rate, heart rate or temperature, decreased blood pressure or oxygen saturation levels or altered mental state. Using TTS/EWS in maternal critical care is thus predicated on the notion that careful and regular monitoring of maternal physiological parameters, as indicators of maternal well-being, will assist in the early recognition of compromise in a pregnant woman (NCEC/HSE 2014). This, in turn, will lead to appropriate escalation of care and early intervention in an effort to reduce or avoid maternal mortality or morbidity. Furthermore, there is the added aspiration that the use of TTS/EWS might improve aspects of clinical governance, especially considering that a significant proportion of maternal deaths are linked to substandard care (CMACE 2011).

Description of the intervention

TTS/EWS are bedside physiological assessment protocols, charts or tools designed to record routinely assessed clinical parameters; that is, blood pressure, temperature, heart rate, respiration rate, urine output and mental/neurological alertness. While subtly different or modified versions of TTS/EWS exist in practice (Bick 2014; Isaacs 2014; Shields 2016; DOH 2019), in general, these systems, which are administered and completed by clinicians (midwives, obstetricians, etc.), involve the application of scores or alert indicators to the observed physiological parameters, based on their prespecified limits of normality. Developed systems are adapted for use at the local level or specific systems might be recommended for use in national clinical guidelines (e.g. DOH 2019). In a UK survey of National Health Service (NHS) organisations, for example, on the extent of EWS used, 66% (69/104) reported that they used their own adapted EWS, 31% (32/104) the CEMACH (confidential enquiry into maternal and child health) example (Lewis 2007) and 3% reported using another form of EWS (Bick 2014). In a further survey of 222 maternity units in the UK, in which nine units returned samples of the EWS they used, numerical scores (0, 1, 2) were applied to physiological parameters outside of prespecified cut-off values in 44% (4/9) of EWS, while the remaining five units used an EWS with a colour-coded system (red, yellow or green indicators based on observed values) (Swanton 2009). While single-parameter systems may exist, the majority of systems include multiple parameters, with the summated chart 'score' or colour zones used to assist the maternity care provider identify the need to escalate care. Communication tools, such as SBAR, (Situation, Background, Assessment, Recommendation) which provides a structured method for communicating critical information (Institute for Healthcare Improvement 2017), are often used in combination or as an adjunct to a TTS/EWS to ensure an effective and meaningful call for assistance and escalation of care.

The various TTS/EWS used in clinical practice have a common objective in the early recognition and escalation of care; however, they can vary slightly with regard to the physiological parameters that they assess. For example, in three studies that reviewed EWS charts from UK maternity units, the parameters of heart rate, respiration rate, blood pressure, temperature and arterial oxygen saturation (SaO_2) were identified as being included in 100% (192/192) of charts while neuroresponse/conscious level was included in 57% (109/192), urine output in 81% (156/192), pain score in 22% (42/192), proteinuria in 38% (73/192), 'looks unwell' in 12% (23/192) and capillary refill in 20% (38/192) (Swanton 2009; Bick 2014; Isaacs 2014). Separate systems have been developed for use in infants and paediatric settings, and their effectiveness reviewed (Lambert 2017).

How the intervention might work

TTS/EWS are based on the premise that adverse physiological changes occur before or early in a situation of clinical deterioration. Thus, by using these systems, changes that might be indicative of clinical deterioration or emerging maternal critical illness are highlighted to maternity care providers early in the evolution of disease. This, in turn, may allow for intervention(s) to alter the course of the emerging critical illness, and ultimately reduce, or avoid, mortality and morbidity sequelae. To achieve this, the TTS/EWS must be used consistently and routinely when a pregnant or postpartum woman is directly under the care of the maternity care providers/service. A number of studies, however, have demonstrated significant variance in compliance rates with TTS/EWS use, ranging from below 50% in three studies (Allman 2010; Waldron 2010; Hunjan 2013) to 82% in one study (Maguire 2015), and 100% in two studies (Bapir 2013; Ram 2013).

Furthermore, compliance with TTS/EWS appears to diminish over the duration of a woman's in-hospital stay. For example, the

number of maternity EWS where no observations were recorded over a number of consecutive hours ranged from 64% for two hours to 2% for seven hours in one study (Allman 2010), and from 11% 'poor' recordings at one-hour postoperative to 27% at two hours and a 91% 'poor' recordings from three to 24 hours postoperatively (Helme 2012). Of further concern, in one audit, 40% of maternity EWS scores were found to be inaccurate (Isaacs 2014). Barriers to successful implementation and use of EWS have been identified as overlap with other charts, lack of training in EWS use, lack of support for EWS, staff shortages, too time consuming and lack of evidence and validation (Bick 2014; Isaacs 2014).

Contrastingly, the introduction of an EWS, however, does appear to help improve physiological parameter assessments. For example, in O'Connor 2010, four-hourly observations improved on all parameters after the introduction of a maternity EWS as follows: blood pressure from 20% to 93%, heart rate from 20% to 93%, respiration rate from 8% to 74%, SaO_2 from 7% to 66% and temperature from 18% to 97%. Furthermore, a maternity EWS chart was described as 'may have been useful' in 77% (84/109) of cases of maternal compromise, and late detection of illness decreased from 23% (7/31 cases) to 10% (3/29 cases) after the introduction of EWS, with the largest reduction in late detection seen in obstetric haemorrhage (from 16% to 5%) (Treadgold 2010).

Why it is important to do this review

While there is some evidence to suggest that physiological TTS/EWS may be useful in predicting morbidity (Carle 2013; Maguire 2015; Shields 2016), and while these systems are increasingly being recommended for use in maternity care, concerns have also been expressed about the lack of validated systems for use in maternity populations (Mackintosh 2014), and of those conducted the majority focus on high-risk populations (Paternina-Caicedo 2017; Ryan 2017). This raises questions as to the clinical effectiveness of such systems, in particular, for reducing maternal and neonatal morbidity and mortality in maternity populations. For this reason, the synthesis of evidence of the clinical effectiveness of TTS/EWS is required.

OBJECTIVES

To evaluate the clinical- and cost-effectiveness of maternal physiological TTS/EWS on pregnancy, labour and birth, postpartum (up to 42 days) and neonatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised and quasi-randomised controlled trials (RCTs), including cluster-RCTs, comparing physiological TTS/EWS with no system or another system. We included studies published in abstract format if they reported sufficient information, or where we could obtain the required information from the authors. Studies using an individual cross-over design were not eligible for inclusion in this review.

Types of participants

Women who were pregnant or who had given birth at any gestation within the previous 42 days, at high risk and low risk for pregnancy, labour and birth, and postpartum complications, as described or defined as such by the study authors.

Types of interventions

Physiological TTS/EWS, which rely on periodic observation of selected basic physiological clinical parameters (blood pressure, heart rate, respiration rate, temperature, etc.) with predetermined calling or response criteria for escalating care to facilitate prompt recognition of clinical deterioration.

We considered escalation protocols or communication tools used in combination with, or as an adjunct to the TTS/EWS, e.g. the ISBAR (Identity, Situation, Background, Assessment and Recommendation) communication tool (Lewis 2007); however, we did not find any studies exclusively on these.

Comparators were the use of TTS/EWS versus non-use of a system. We would also have included the use of a TTS/EWS versus the use of an alternative TTS/EWS, but we did not find any studies evaluating this comparator.

Types of outcome measures

Primary outcomes

- Maternal death

Secondary outcomes

Maternal

- Maternal critical illness, as measured separately by any of the following:
  - maternal collapse (cardiac or respiratory arrest);
  - haemorrhage (antepartum or postpartum, estimated blood loss more than 500 mL);
  - sepsis;
  - eclampsia; and
  - HELLP (haemolysis, elevated liver enzymes and low-platelet count) syndrome
- Admission to intensive care unit (ICU)
- Length of hospital stay (days)
- Maternal anxiety (using a validated measuring tool)

Neonatal

- Perinatal death (death up to 28 days postpartum)
- Apgar score less than 7 at five minutes of age
- Admission to neonatal intensive care unit (NICU)/special care baby unit (SCBU)
- Length of stay in NICU/SCBU (days)
- Hypoxic ischaemic encephalopathy
- Economic
- Cost-effectiveness measures, as measured by any of the following:
  - direct healthcare professional resource use (staff time, education input, additional referrals, etc.);
  - incremental cost-effectiveness ratios; or
  - quality-adjusted life years.

Search methods for identification of studies

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (28 May 2021).

The Register is a database containing over 27,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies, Excluded studies).

In addition to the search carried out by the Information Specialist, we searched the OpenGrey database to identify grey literature and the ProQuest Dissertations and Theses database to potentially retrieve dissertation theses reporting on trials related to our topic of interest (7 June 2021). We also searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (7 June 2021) (see Appendix 1 for search terms used).

Searching other resources

We reviewed the reference lists of all selected papers to identify any additional, potentially eligible studies not captured by the electronic searches. We also contacted experts in the field to identify any unpublished studies but this did not reveal any further studies not already identified by our search of electronic sources.

We did not apply any language or date restrictions.

Studies that were reported as abstracts only would have been included where there was sufficient detail reported in the abstract to assess the study's eligibility for inclusion in the review and sufficient data provided to extract for analysis, or if we could obtain the required information from the authors; however, as no studies in abstract format only were identified, this did not apply.

Data collection and analysis

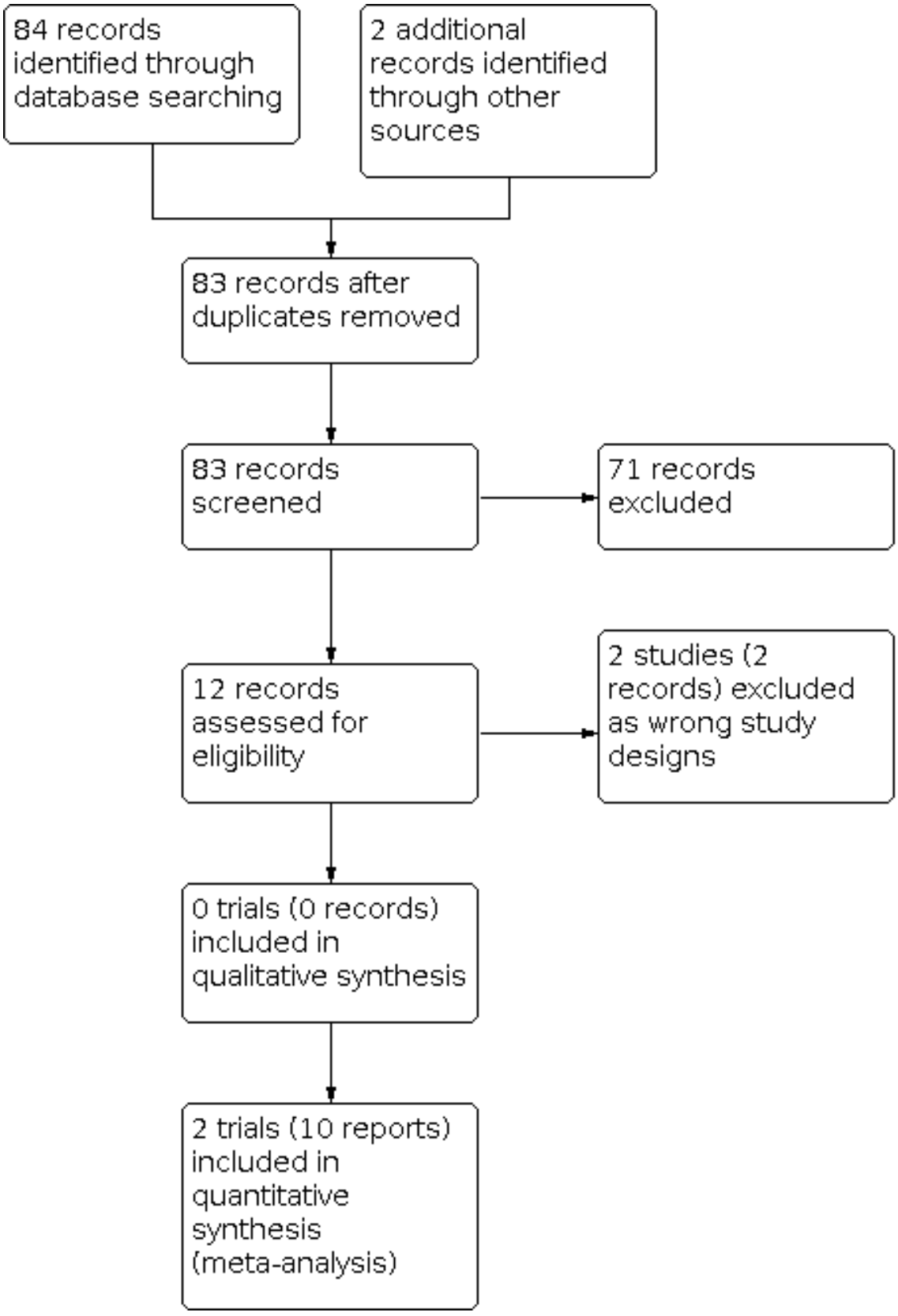
The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two review authors (VS and MN) independently assessed for inclusion all the potential studies identified as a result of the search strategy. Any disagreement was resolved through discussion. For one study we were uncertain of the trial design, and consulted a third review author (DD) to ascertain a third opinion (Shields 2016). We also contacted the author of the study to clarify the study's design, and received a reply indicating that the study was a non-randomised trial, with sites selected based on preference for intervention or control. This confirmed that the study did not meet our study design inclusion criterion.

We created a PRISMA study flow diagram to map the number of records identified, included and excluded (Liberati 2009; Figure 1).

Figure 1. Study flow diagram.



Screening eligible studies for trustworthiness

All studies meeting our inclusion criteria were evaluated by two review authors (VS and MN) against the Cochrane Pregnancy and Childbirth Trustworthiness Screening tool (CPC-TST). This screening tool is a set of predefined criteria to select studies that, based on available information, are deemed to be sufficiently trustworthy to be included in the analysis. The criteria are as follows.

Research governance

- No prospective trial registration for studies published after 2010 without plausible explanation
- When requested, trial authors refuse to provide/share the protocol and/or ethics approval letter
- Trial authors refuse to engage in communication with the Cochrane Review authors
- Trial authors refuse to provide IPD data upon request with no justifiable reason

Baseline characteristics

- Characteristics of the study participants being too similar (distribution of mean, i.e. standard deviation (SD) excessively narrow or excessively wide, as noted by Carlisle 2017)

Feasibility

- Implausible numbers (e.g. 500 women with severe cholestasis of pregnancy recruited in 12 months)
- (Close to) zero losses to follow-up without plausible explanation

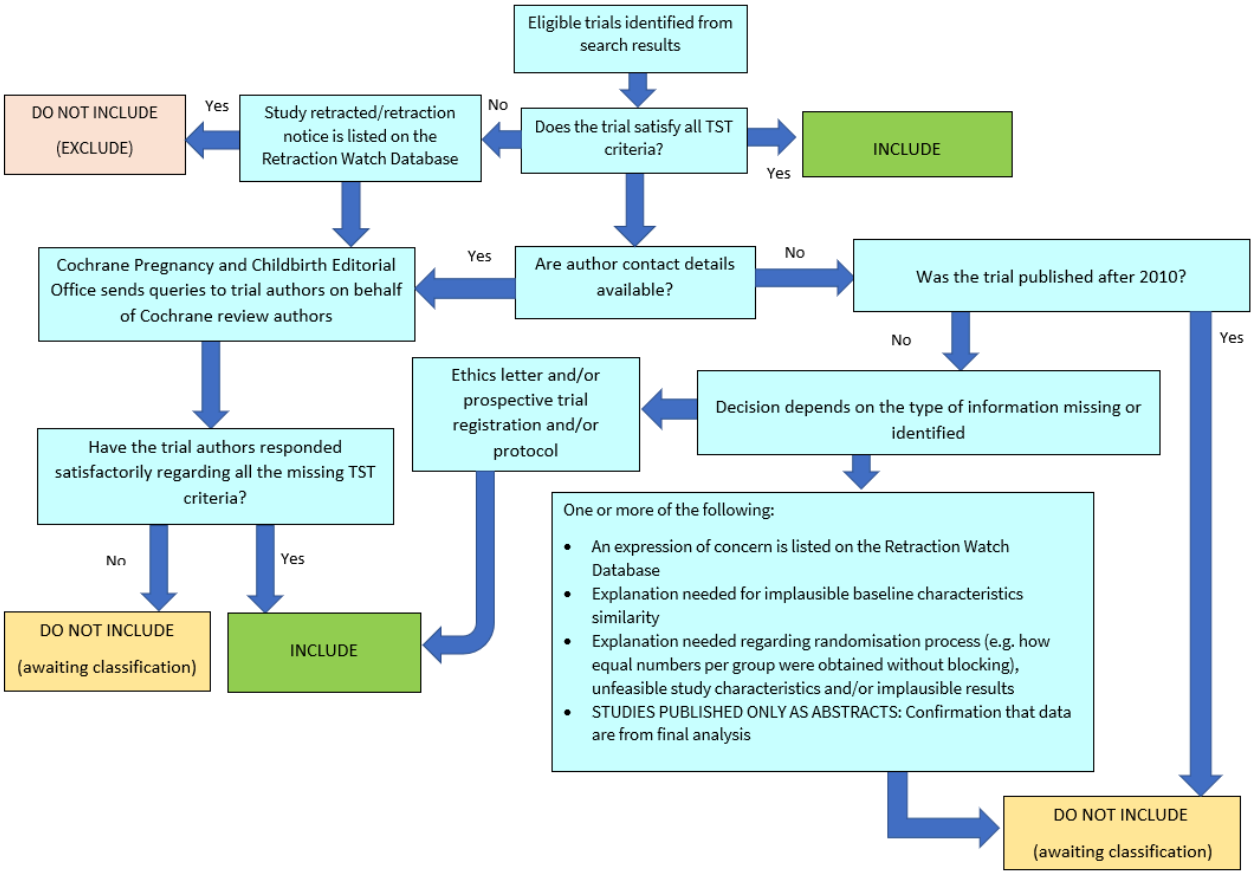
Results

- Implausible results (e.g. massive risk reduction for main outcomes with small sample size)
- Unexpectedly even numbers of women 'randomised' including a mismatch between the numbers and the methods, e.g. if they say no blocking was used but still end up with equal numbers, or they say they used blocks of 4 but the final numbers differ by 6

Studies assessed as being potentially 'high risk' would not have been included in the review; however, all eligible studies were classified as low risk. If a study had been classified as 'high risk' for one or more of the above criteria we would have attempted to contact the study authors to address any possible lack of information/concerns. If adequate information remained unavailable, the study would have remained in 'awaiting classification' and the reasons and communications with the author (or lack of) described in detail.

The process is described in Figure 2.

Figure 2. Process for using the Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool (CPC-TST)



Abstracts

Data from abstracts would have been included where, in addition to the trustworthiness assessment, the study authors confirmed in writing that the data to be included in the review had come from the final analysis and would not change. If such information had not been available/provided, the study would have remained in 'awaiting classification' (as above). As no eligible studies reported in abstract format only were identified, this did not apply.

Data extraction and management

We extracted data using a specially designed data extraction template including:

- study location and dates study conducted;
- aim of study;
- study design;
- description of study sample including numbers involved;
- description of TTS/EWS used;
- reported outcomes;
- study results;
- sources of funding; and
- any reported conflicts of interest.

We extracted data on the review's prespecified outcomes for reported outcomes that occurred after randomisation of participants. For example, if a study enrolled postpartum women and the occurrence of maternal critical illness or perinatal death was before randomisation to the study, we would not have considered these data in our analyses. For eligible studies, two review authors (VS and MN) extracted the data using the agreed form. When information regarding any of the above was unclear, we contacted the authors of the original reports for further details as required.

Assessment of risk of bias in included studies

Two review authors (VS and MN) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We resolved any disagreement by discussion and would have involved a third assessor (JS or LK) had this been necessary, but this was not required.

We assessed risk of bias for randomised trials as per the criteria (1) to (7) below. As we included a cluster-randomised trial (Vousden 2019), we also used appropriate methods for assessing additional bias in this design (i.e. recruitment bias, baseline imbalance, loss of clusters, incorrect analysis and comparability with individually randomised trials) as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. alternate, odd or even, date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we re-included missing data in the analyses that we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);

- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as-treated' analysis done with substantial departure of intervention received from that assigned at randomisation; a cut-off value of 20% of missing data will be used to determine high risk of bias);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest have been reported incompletely and so cannot be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias; for example, early stopping of study.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2017). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We had planned to explore the impact of the level of bias through undertaking sensitivity analyses (see Sensitivity analysis), however, this was not required.

Measures of treatment effect

Dichotomous data

For dichotomous data (e.g. maternal death), we had originally planned to present the results as summary risk ratios (RRs) with 95% confidence intervals (CIs). As we included a cluster-randomised trial that reported their adjusted outcome data as odds ratio (OR) (see Unit of analysis issues), we present the results as summary ORs with 95% CIs, and have noted this change in the Differences between protocol and review section of the review.

Continuous data

For continuous data (e.g. length of hospital stay), we used the mean difference (MD) with 95% CI as the outcome was measured in one included study only. In future updates where more than one study measures the same outcome, but uses different methods (e.g. different measurement scales), we will use the standardised mean difference (SMD) with 95% CI to combine the trials' outcome data.

Unit of analysis issues

Cluster-randomised trials

We identified one cluster-randomised trial on the topic and included this trial in the analyses along with an individual randomised trial. We sought statistical advice from K Dwan (Cochrane Methods Support unit lead and Statistical Editor) as we had planned to adjust the sample size of the cluster trial using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population (Higgins 2011). As the trial used appropriate analyses methods in adjusting for cluster effects, we considered it reasonable to combine the trial's data (adjusted OR, bent stick model) using the generic inverse variance method with that of the included individual randomised trial's data for outcomes reported in both studies where it was reasonable to combine these in a meta-analysis. In future updates, if new cluster trials are included, we may need to revert to adjusting the sample sizes of the cluster trials using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the reported data are appropriately adjusted we may be able to combine data using the generic inverse variance method. In either case, we will seek expert statistical advice prior to undertaking the analyses.

Cross-over trials

We did not anticipate individual cross-over trials on this topic, nor did we identify any.

Studies with multiple intervention groups

We did not identify studies that included multiple interventions (e.g. different types of TTS/EWS) and comparison groups. If we had identified and included studies of this type, for purposes of analyses, we would have combined all relevant intervention groups into a single group and combined all relevant control groups into a single control group to create single pair-wise comparisons (see section 16.5.4 of *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2011).

Multiple pregnancies

We considered that included studies may potentially involve women with multiple pregnancies. To address this we used the number of babies as the denominator for analyses of neonatal outcomes as required, whereas for maternal outcomes, we used the number of women as the denominator.

Dealing with missing data

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis; that is, we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each study was the number randomised minus any participants whose outcomes were known to be missing.

We contacted study authors to ask them to provide missing outcome data. Had this not been possible, we would have performed a sensitivity analysis to explore the impact of including such studies in the overall assessment of results. In contacting the author of one of the included studies (Chakravarthy 2019), the reply informed us that there were no withdrawals or losses to follow-up in their study. We did not contact the author of the second study as sufficient information regarding missing data was available in the trial report.

We identified issues regarding the data for some outcomes in the Vousden 2019 study. In this study neonatal death data were collected only in women who had experienced a primary outcome, that is one of maternal death, eclampsia or hysterectomy. Furthermore, Vousden 2019 had a prespecified outcome of cause of death. Data on our prespecified outcomes of haemorrhage and sepsis are available only as cause of death data (i.e. in those women who died) in this study. As the comparison is not between the randomised groups for these conditional outcomes, and because we would not know whether the treatment effect in the population who had died (for haemorrhage and sepsis) or who had a primary outcome (for neonatal death) is similar to that in the whole population, we excluded these conditional data from the review. In future updates, should more eligible studies become available, we will continue to exclude these conditional data.

We had planned to exclude from the analyses data from trials or outcomes that are at high risk of bias due to missing data, for example, those with high levels of missing data or a large number of participants analysed in the wrong group. Cut-off levels for high risk of bias are more than 20% of missing data for the primary outcome of maternal death or more than 20% of participants analysed in the wrong group. We will consider this for future updates of this review.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 (Higgins 2003), and Chi^2 statistics (Deeks 2017). We regarded heterogeneity as substantial if I^2 statistic was greater than 30% and either Tau^2 was greater than zero, or there was a low P value (< 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there had been 10 or more studies in a meta-analysis we would have investigated reporting biases (such as publication bias) using funnel plots. We would have assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we would have performed exploratory analyses to investigate it (Sterne 2017), but this was not required.

Data synthesis

Statistical analysis was conducted using Review Manager 5 software (Review Manager 2020). Due to the varied nature of the outcomes reported in the two studies (see Description of studies), two of our prespecified outcomes only were combined in meta-analyses. As the intervention in the studies varied clinically (paper-based EWS and automated alert EWS), we used a random-effects model for combining these two outcomes. The random-effects summary was treated as the average of the range of possible treatment effects and we discuss the clinical implications of treatment effects differing between trials. If the average treatment effect had not been clinically meaningful we would not have combined the trials' outcome data.

In future updates, if additional studies are included, we will use a fixed-effect meta-analysis for combining outcome data where it was reasonable to assume that studies were estimating the same underlying treatment effect, that is, where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. We will use a random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful when there is clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or where substantial statistical heterogeneity is detected.

Subgroup analysis and investigation of heterogeneity

Had we identified substantial heterogeneity, and identified more than two trials for inclusion, we would have investigated it using subgroup analyses and sensitivity analyses.

We had planned to carry out the following subgroup analyses: use of TTS/EWS versus non-use of a system or use of TTS/EWS versus use of an alternative TTS/EWS in:

- women considered to be high risk for pregnancy, labour and birth, and postpartum complications;
- women considered to be low risk for pregnancy, labour and birth, and postpartum complications.

As there were insufficient studies included with the relevant data we did not perform subgroup analyses. Had we been able to perform subgroup analyses we would have used the primary outcome of maternal death in the analyses, and will consider this in future updates.

If subgroup analyses are applicable in future updates, we will assess subgroup differences by interaction tests available within Review Manager 5 (Review Manager 2020), and report the results of these analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

Had it been relevant, we would have carried out sensitivity analyses to explore the effect of trial quality for important outcomes in the review, and will consider this in future updates if applicable. Where there is high risk of bias associated with the domain of allocation concealment, random sequence generation, incomplete outcome data and selective reporting of the Cochrane tool for assessing risk of bias (Higgins 2017), we will explore this by sensitivity analyses in future updates if appropriate. We will use the primary outcome of maternal death in any future sensitivity analysis. If appropriate, we will also carry out sensitivity analysis to explore the effects of fixed-effect or random-effects analyses for outcomes with statistical heterogeneity and the effects of any assumptions made, such as the value of the ICC used for cluster-randomised trials.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach as outlined in the GRADE handbook in order to assess the certainty of the body of evidence relating to the following outcomes

(where reported) for the main comparisons of TTS/EWS versus no system (Schünemann 2013):

- maternal death:
- maternal critical illness, as measured separately, by any of the following:
  - maternal collapse (cardiac or respiratory arrest)
  - haemorrhage (antepartum or postpartum, estimated blood loss more than 500 mL)
  - sepsis
  - eclampsia, and
  - HELLP (haemolysis, elevated liver enzymes and low-platelet count) syndrome;
- maternal admission to ICU;
- perinatal death (death up to 28 days postpartum).

We used the GRADEpro Guideline Development Tool (GRADEpro GDT 2015) to import data from Review Manager 5 (Review Manager 2020) to create Summary of findings 1 (based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017)). We used the GRADE approach to produce a summary of the intervention effect and a measure of certainty for each of the above outcomes, other than maternal collapse and perinatal death which were not reported in the two included studies. For perinatal death, we used neonatal death instead in Summary of findings 1 as data on neonatal death were available. We provided the rationale and an explanation for this choice in a footnote in the table.

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome. The evidence can be downgraded from 'high certainty' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. For each assumed risk cited in the table, we provided a source and rationale, and we used the GRADEpro GDT profiler system to rank the certainty of the evidence.

RESULTS

Description of studies

Results of the search

Figure 1 presents the results of the search and selection process. We retrieved 86 records; 84 from searching the electronic databases and two from additional sources. Three of these records were duplicate records and were excluded. We screened the remaining 83 records on title and abstract and excluded 71 of these as they were clearly not eligible. We assessed the full texts of the remaining 12 records. We excluded two records (2 studies) based on study designs; one was a before-and-after study (Daly 2011), and the other a non-randomised cluster trial with intervention sites selected based on site preference (Shields 2016). We included two trials reported across 10 records (Chakravarthy 2019; Vousden 2019). Of these, the Vousden 2019 study is reported across eight records which includes records of the protocol, pretrial feasibility activity, process evaluation, the main trial report, and secondary analyses reports that focus further on pregnancy-related death and obstetric haemorrhage outcome data (see Included studies for list of associated publications).

Screening eligible studies for trustworthiness

We screened Chakravarthy 2019 and Vousden 2019 against the Cochrane Pregnancy and Childbirth Trustworthines Screening Tool and assessed both studies as low risk.

Included studies

Design

The included studies reported on a single-centre parallel randomised (1:1) controlled trial (Chakravarthy 2019), and a multicentre stepped-wedge cluster (10 clusters) randomised trial (Vousden 2019).

Sample sizes

The combined sample sizes of the two included studies was 536,933. Chakravarthy 2019 included 700 women; 340 in the intervention group and 360 in the control group. Vousden 2019 included 536,233 women; 247,238 in the intervention group and 288,995 in the control group.

Setting and trial dates

Chakravarthy 2019 conducted their study in a `single-centre`, subspeciality tertiary obstetric care institute in India, which lacks multispeciality, multidisciplinary care facilities. The study was carried out over a one-year period from February 2017 to February 2018. Vousden 2019 conducted their study in 10 purposely selected low-resource settings. These were Addis Ababa in Ethiopia, Cap Haitien in Haiti, Freetown in Sierra Leone, Harare in Zimbabwe, Gokak in India, Kampala and Mbale in Uganda, Lusaka and Ndola in Zambia, and Zomba plus the Southern Region in Malawi. Each cluster comprised of at least one urban or peri-urban secondary or tertiary health facility that provided comprehensive emergency obstetric care with multiple peripheral facilities that referred to the central hospital. Overall, the 10 clusters comprised 232 primary facilities, 44 secondary facilities and 10 tertiary facilities. The study was carried out over 20 months from April 2016 to November 2017.

Participants

Participants in the Chakravarthy 2019 study were pregnant women of all ages between six weeks' gestation and up to six weeks' postpartum, American Society of Anaesthesiologists Grade I-Grade IV, admitted to the obstetric wards of the study institute. Pregnant women managed as outpatients, women admitted for termination of pregnancy or miscarriage or tubectomy, or women ≥ six weeks' postpartum were excluded. Participants in the Vousden 2019 study were all women identified as pregnant or within 42 days of having given birth, presenting for maternity care in a cluster facility or to community healthcare providers (HCPs). All HCPs working in the cluster facilities had access to the intervention. This included community HCPs who were involved in providing routine maternity care and were supported at the district level. No exclusion criteria were applied.

Interventions and comparison

We used the TIDieR checklist in describing the interventions in the two included studies (Hoffmann 2014).

Chakravarthy 2019 evaluated the Saving Mothers Score (SMS) and compared it with standard care. Standard care is described as management according to the existing hospital protocols for care, although these protocols were not further described. The SMS intervention was developed for early identification of at-risk pregnant women based on a combination of pregnancy-related risk factors, physiological variables and biochemical tests. The scoring system of the SMS was based on the modified early obstetric warning score (MEOWS) and was made more comprehensive by including 33 items pooled into three parameters; i) pregnancy-related risk factors, ii) physiological variables, and iii) biochemical tests. Pregnancy-related risk factors were assigned one of two colours (orange denotes a risk factor and green indicates no risk) with simple yes or no response options. A score of one was assigned to an identified risk factor. The presence of ≥ four oranges at any time during pregnancy indicates a high-risk pregnancy. Eight physiological parameters were included in the SMS. These were blood pressure, temperature, pulse, respiratory rate, oxygen saturation, urine output, pain and neurological status of the woman. All parameters outside of normalcy were given a score of one, other than respiratory rate and conscious level which were both given scores of two. The boundaries of what constituted a normal or abnormal parameter reading, however, were not described. Eight biochemical parameters were included and assigned scores depending on the severity of derangement. A healthy pregnant woman was colour-coded as green with a score of zero to three. Those needing high-dependency unit care or deemed at moderate risk were colour-coded orange and had a score of three to five. Sick pregnant women, at high risk and needing intensive care unit (ICU) care were colour-coded red and had a score of ≥ six. Training of healthcare providers on use of the SMS is not described. The schedule for assessing the clinical parameters in the SMS is described as on admission and at 6-, 12-, 24-, 36- and 48-hour intervals. Intervention adherence and fidelity information were not provided.

Vousden 2019 evaluated the CRADLE vital signs alert (VSA) and training package and compared it with standard care. Standard care is described as the use of various medical devices (e.g. pre-existing blood pressure monitoring with a variety of devices) and management as per local guidelines. The Microlife CRADLE VSA device is a hand-held, upper-arm, semi-automated device that measures blood pressure and pulse. The device has been subjected to extensive testing for accuracy and is validated as accurate for use in pregnancy. The device incorporates a traffic light (red, yellow, green) EWS that alerts all levels of HCPs, including those without formal training, to abnormalities in blood pressure and pulse secondary to obstetric haemorrhage, sepsis and pregnancy hypertension. The thresholds that trigger the traffic lights were determined through prediction studies; a red light indicates that immediate action or referral should be initiated, a yellow light indicates a less urgent need for action or referral, and a green light indicates that no action other than usual care is required. The CRADLE VSA was incorporated into routine maternity care as part of the intervention. Primary, secondary and tertiary facilities were allocated devices according to their birth rate, staffing numbers and number of beds per ward. Pre-existing blood pressure measurement devices were removed from clinical areas unless existing equipment had functionality designed for that area, e.g. repeated automated measures in an operating theatre or a high-dependency unit, and this was left to the discretion of the lead clinician. As part of the intervention, the CRADLE research group created a simple CRADLE training package for prospective CRADLE VSA users. The training package consisted of short animated films, an interactive session, action prompt cards attached to the CRADLE VSA and posters. There were two sets of training materials available, one for facility HCPs and one for community HCPs with very limited resources or no formal training. All materials were translated into the local language where required. The CRADLE package content covered: how to use the CRADLE VSA, maintenance of the CRADLE VSA and basic overview of clinical assessment and management of pre-eclampsia/eclampsia and shock in relation to the traffic light alerts. At the time of randomisation the local implementation team (clinical research officers responsible for ongoing CRADLE outcome data collection and site principal investigators) attended face-to-face one-off training with the research team lasting approximately five hours. The implementation team and research team subsequently delivered one-off group training sessions lasting two to four hours to local stakeholders and representative HCPs from each of the clinical areas in the cluster. Attendees were given training materials and CRADLE VSA to disseminate to their clinical areas. The implementation team continued to visit clinical areas regularly to collect outcome data therefore providing ongoing support to HCPs. The core components of the intervention (the CRADLE VSA, animated films, posters and content of the training presentation) were standardised across all clusters. Implementation and fidelity were assessed at three months and six to nine months after implementation. Uptake and acceptability of the intervention was described as "good" and 61% of healthcare providers were trained in the intervention.

Outcomes

The included studies reported on the review's prespecified outcomes as follows: maternal death (Chakravarthy 2019; Vousden 2019), total obstetric haemorrhage (Chakravarthy 2019), antenatal haemorrhage (Chakravarthy 2019), postpartum haemorrhage (defined as estimated blood loss of > 500 mL) (Chakravarthy 2019), sepsis (Chakravarthy 2019), eclampsia (Chakravarthy 2019; Vousden 2019), HELLP (Chakravarthy 2019), admission to ICU (Chakravarthy 2019; Vousden 2019), length of maternal hospital stay in days (Chakravarthy 2019), neonatal death (not defined) (Chakravarthy 2019), Apgar score < 7 at five minutes of age (Chakravarthy 2019), and admission to NICU/SCBU (Chakravarthy 2019).

As discussed in the Dealing with missing data section, some outcomes in the Vousden 2019 study were reported as conditional outcomes only, and were thus excluded from the review. These outcomes were obstetric haemorrhage as a cause of death, sepsis as a cause of death, neonatal death (up to 28 days postpartum) in women with a primary outcome (i.e. a composite of maternal mortality and morbidity) and stillbirth in women with a primary outcome.

The following prespecified outcomes were not reported in either of the two included studies: maternal collapse, maternal anxiety, perinatal death, length of stay in NICU/SCBU, hypoxic ischaemic encephalopathy, and cost-effectiveness measures. Although perinatal death was not measured in the two studies, Chakravarthy 2019 reports on neonatal death (undefined); we present the results for neonatal death in the review.

Sources of trial funding

The Chakravarthy 2019 report does not provide details of study funding sources; however, details in the trial registry (Clinical Trials Registry India; CTRI/2018/01/011219), under "sources of monetary or material support", indicate that Niloufer Hospital for Women and Children, Osmania Medical College, Hyderabad supported the study. The Vousden 2019 trial was funded by the UK Medical Research Council, Indian Department of Biotechnology, and UK Department of International Development Global Research Programme (MR/N006240/1). Two of the trial authors (JS and PTS) are supported by the UK National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital National Health Service Foundation Trust. A third trial author (LCC) is supported by a NIHR Research Professorship (RP-2014-05-019).

Trial authors' declarations of interest

The trial authors of both studies declare no conflicts of interest.

Excluded studies

We excluded two studies, reported across two records. Daly 2011 conducted a retrospective before-and-after study in Ireland to assess maternal morbidity management over two six-month periods pre- and post-introduction of a Physiological Observation Track and Trigger System (POTTS) to validate its use. Shields 2016 conducted a pilot non-randomised cluster trial in the USA to determine if maternal morbidity could be reduced with the implementation of a clinical pathway-specific Maternal Early Warning Trigger (MEWT) tool. The tool was implemented in six of 29 hospitals based on hospital preference for evaluating the intervention.

Risk of bias in included studies

Summary risk of bias assessments are presented in Figure 3 and Figure 4.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

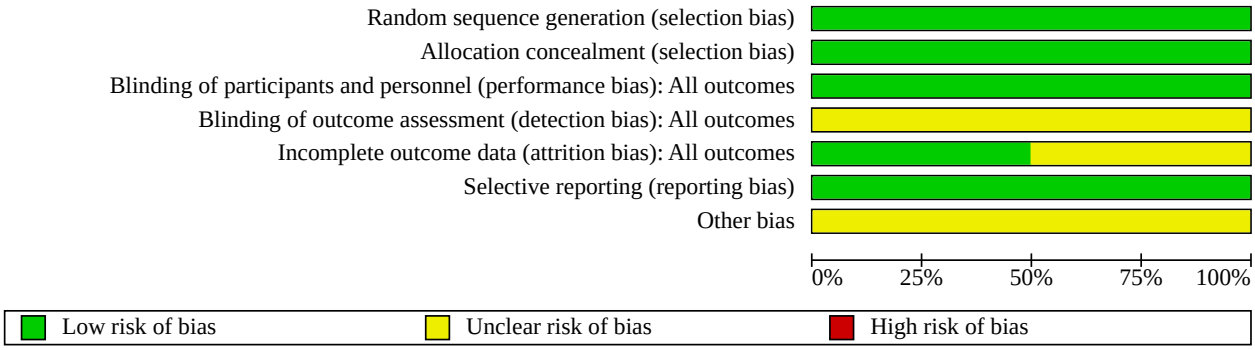
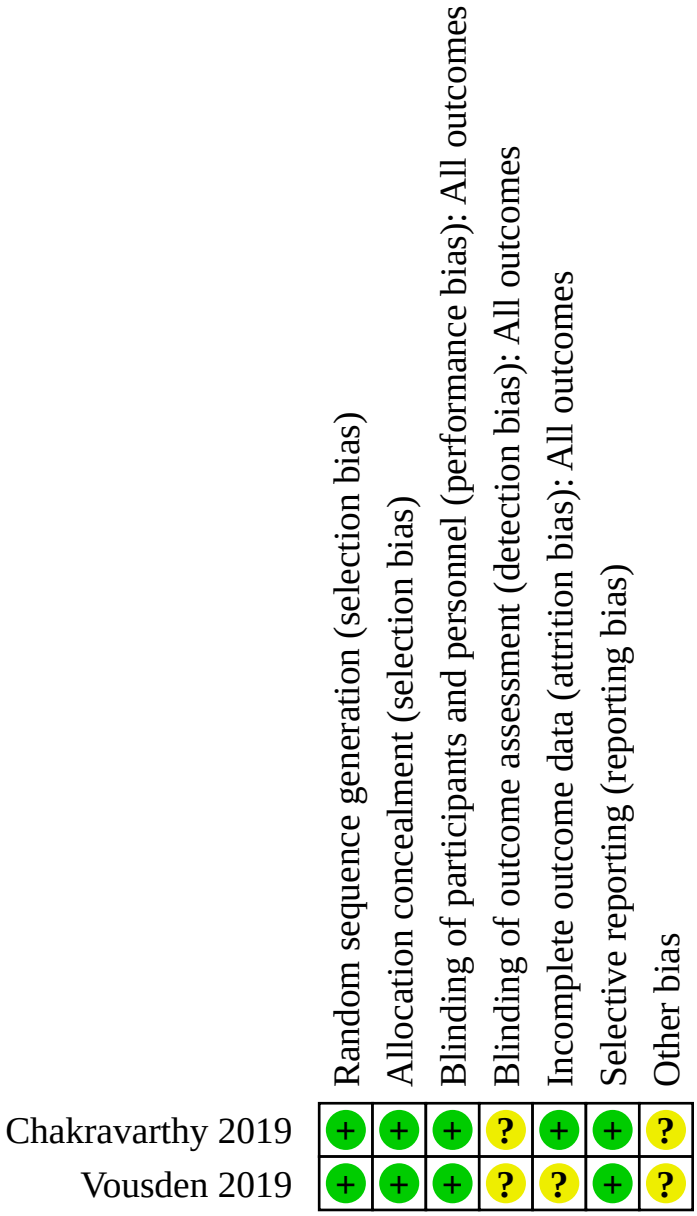


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The two included studies used computer-generated random allocation in determining the allocation sequences in their trials, and we assessed them as low risk of bias on random sequence generation. We also assessed both studies as low risk of bias on allocation concealment; Chakravarthy 2019 used sequentially sealed opaque envelopes, opened by a nurse not related to the study after eligibility for enrolment was confirmed. In Vousden 2019, the clusters were masked to allocation until two months before they were due to receive the intervention; the two month unmasked period was time used to facilitate intervention training.

Blinding

We assessed both Chakravarthy 2019 and Vousden 2019 as low risk of bias on blinding of participants and personnel. Chakravarthy 2019 indicated that all participants were masked to the group allocations, although personnel administering the intervention

were unblinded due to the nature of the intervention. The outcomes measured in the study were objective measures and were unlikely to be influenced by a lack of blinding. In Vousden 2019 although blinding of participants and personnel was not possible due to the nature of the intervention, we assessed this as low risk of bias as all of the review's prespecified outcomes measured in this study were objective outcome measures, and were thus minimally prone to performance bias. For detection bias (blinding of outcome assessment), we assessed both Chakravarthy 2019 and Vousden 2019 as unclear risk of bias as no information was provided as to who precisely analysed the data.

Incomplete outcome data

We assessed Chakravarthy 2019 as low risk of attrition bias as there was no evidence in the study report of loss to follow-up or withdrawals. We assessed Vousden 2019 as unclear risk of attrition bias. Although reasons for loss to follow-up in some perinatal outcomes are provided in the study report, the authors also state "*..because IPD were only collected for women with a primary outcome, we had to treat all other women as having no event and therefore had no information from which to estimate the extent of missing data*" (p.e351). Furthermore, for two of our review's prespecified outcomes, haemorrhage and sepsis, Vousden 2019 report these as cause of death data only. Although not exactly missing data, it did mean that for these outcomes the denominator was substantially reduced; that is the number of women who had haemorrhage and sepsis is reported only in women who had another outcome of maternal death. As such, we would be unable to assess whether the treatment effect in the population that is reported (i.e. women who have died) is similar to that in the whole population.

Selective reporting

There was no evidence of selective outcome reporting in either of the two included studies, and we assessed both as low risk of reporting bias. All outcomes prespecified in the protocols and methods sections of the two study reports were reported in the results.

Other potential sources of bias

We assessed the two included studies as unclear risk on other potential sources of bias. In Chakravarthy 2019 the anaesthesiologist involved in providing care to women at the study site was also the study's principal investigator (PI), and was responsible for enrolling women to the study. The author's of the study acknowledge that the anaesthesiologist might have enhanced the care in the SMS group as the anaesthesiologist was not blind to group allocation. In the stepped-wedge cluster trial (Vousden 2019), implementation of the intervention and outcome data collection was by the same team. In the community settings of some clusters, clinical outcomes may not have been usually documented prior to the trial. Use of the CRADLE VSA device during the intervention phase of the trial might have resulted in increased reporting of the primary outcome; thus introducing a potential bias against the intervention.

Effects of interventions

See: **Summary of findings 1** TTS/EWS compared to standard care in maternity care

Comparison 1 TTS/EWS versus standard care

Primary outcomes

Maternal death

Maternal death was reported in the two included studies. There were no maternal deaths in the Chakravarthy 2019 study. Vousden 2019 reported a total of 998 maternal deaths in their study. The evidence suggests that TTS/EWS compared to standard care probably makes little to no difference in maternal death (odds ratio (OR) 0.80, 95% confidence interval (CI) 0.30 to 2.11; 1 study, 536,233 participants; moderate-certainty evidence; Analysis 1.1).

Secondary outcomes

Maternal critical illness

Maternal critical illness as measured separately by:

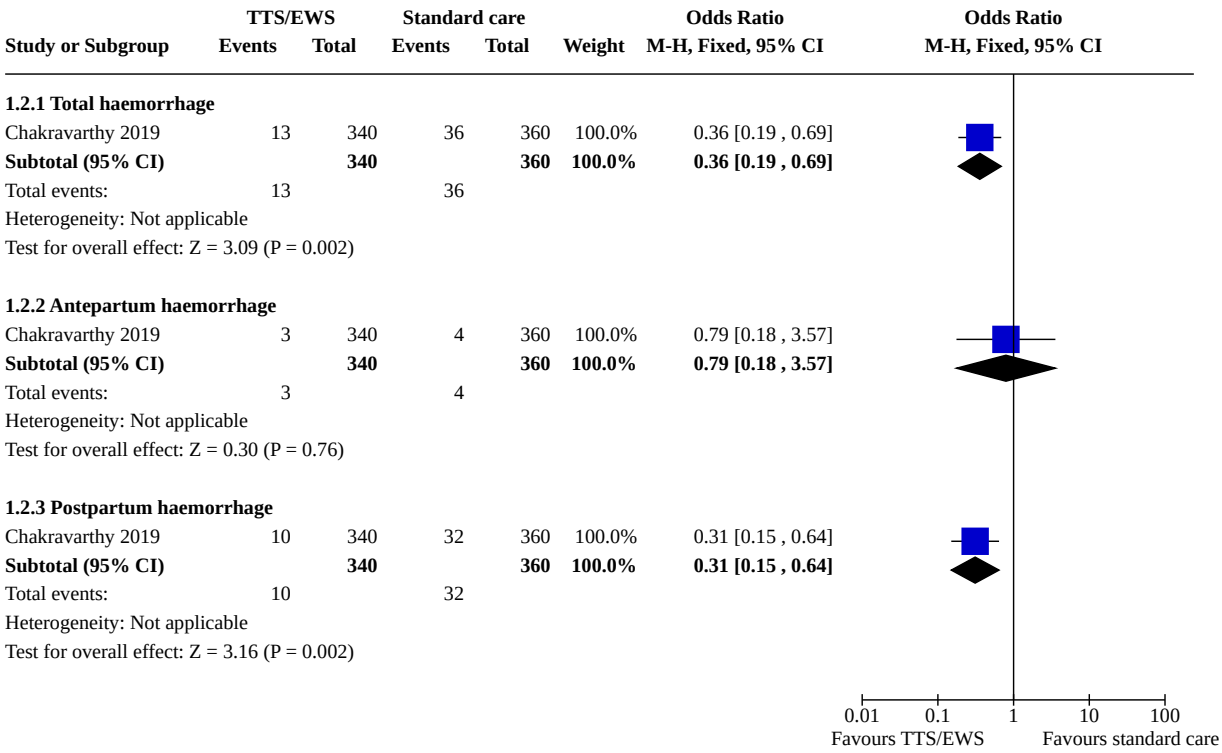
Maternal collapse (cardiac or respiratory arrest)

Maternal collapse was not measured in either of the two included studies.

Haemorrhage (antepartum or postpartum, estimated blood loss more than 500 mL)

Chakravarthy 2019 reported total obstetric haemorrhage and rates of haemorrhage separately by categories of antepartum and postpartum haemorrhage (defined as estimated blood loss > 500 mL). The evidence suggests that TTS/EWS compared to standard care may reduce total haemorrhage (OR 0.36, 95% CI 0.19 to 0.69; 1 study, 700 participants; low-certainty evidence; Analysis 1.2, Figure 5) and may reduce postpartum haemorrhage (OR 0.31, 95% CI 0.15 to 0.64; 1 study, 700 participants; low-certainty evidence; Analysis 1.2, Figure 5), but may make little to no difference on antepartum haemorrhage (OR 0.75, 95% CI 0.18 to 3.57; 1 study, 680 700participants; low-certainty evidence; Analysis 1.2, Figure 5).

Figure 5. Forest plot of comparison: 1 Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, outcome: 1.2 Haemorrhage.



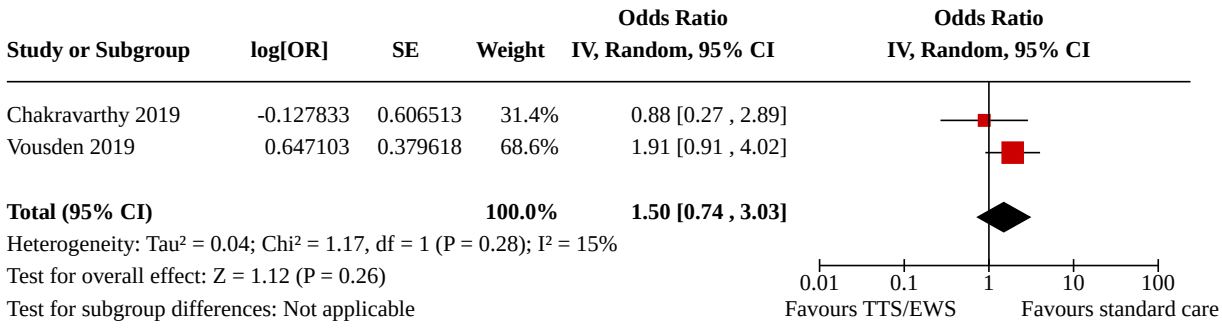
Sepsis

The outcome sepsis was measured in Chakravarthy 2019. The evidence suggests that TTS/EWS compared to standard care may make little to no difference in sepsis (OR 0.21, 95% CI 0.02 to 1.80; 1 study, 700 participants; low-certainty evidence; Analysis 1.3).

Eclampsia

The outcome eclampsia was measured in both included studies. The evidence suggests that TTS/EWS compared to standard care may make little to no difference in eclampsia (OR 1.50, 95% CI 0.74 to 3.03, Tau² = 0.04; 2 studies, 536,933 participants; low-certainty evidence; Analysis 1.4, Figure 6).

Figure 6. Forest plot of comparison: 1 TTS/EWS versus standard care, outcome: 1.5 Eclampsia.



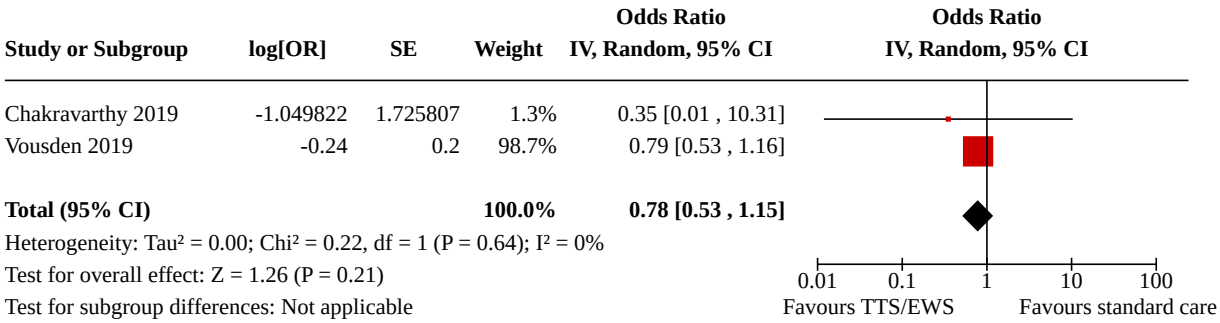
HELLP (haemolysis, elevated liver enzymes and low-platelet count) syndrome

HELLP was measured in Chakravarthy 2019 only. The analysis shows that TTS/EWS compared to standard care may make little to no difference in HELLP (OR 0.21, 95% CI 0.01 to 4.40; 1 study, 700 participants; very low-certainty evidence; Analysis 1.5).

Admission to intensive care unit (ICU)

Admission to ICU was measured in both included studies. The evidence suggests that use of TTS/EWS compared to standard care probably makes little to no difference on the incidence of ICU admission (OR 0.78, 95% CI 0.53 to 1.15, Tau² = 0.00; 2 studies, 536,933 participants; moderate-certainty evidence; Analysis 1.6, Figure 7).

Figure 7. Forest plot of comparison: 1 TTS/EWS versus standard care, outcome: 1.7 Admission to ICU.



Length of hospital stay (days)

One study reported length of hospital stay (Chakravarthy 2019). The evidence suggests that the use of TTS/EWS compared to standard care probably reduces the number of days spent in hospital (mean difference (MD) -1.21, 95% CI -1.78 to -0.64; 1 study, 700 participants; moderate-certainty evidence; Analysis 1.7).

Maternal anxiety (using a validated measuring tool)

Maternal anxiety was not measured in either of the two included studies.

Perinatal death (death up to 28 days postpartum)

Perinatal death was not measured in either of the two studies. Chakravarthy 2019 measured neonatal death (undefined) which we report as a proxy measure of perinatal death. The evidence suggests that TTS/EWS compared to standard care may make little to no difference in neonatal death (undefined) (OR 1.06, 95% CI 0.62 to 1.84; 1 study, 700 participants; low-certainty evidence; Analysis 1.8).

Apgar score < 7 at five minutes of age

One study measured Apgar scores of < 7 at five minutes of age (Chakravarthy 2019). The evidence suggests that TTS/EWS compared to standard care may make little to no difference in Apgars < 7 at five minutes of age (OR 0.58, 95% CI 0.19 to 1.75; 1 study, 700 participants; low-certainty evidence; Analysis 1.10).

Admission to neonatal intensive care unit/special care baby unit (NICU/SCBU)

One study measured admission to NICU (Chakravarthy 2019). The evidence suggests that TTS/EWS compared to standard care may make little to no difference in admission to the NICU/SCBU (OR 0.68, 95% CI 0.42 to 1.11; 1 study, 700 participants; low-certainty evidence; Analysis 1.11).

Length of stay in NICU/SCBU (days)

Length of stay in NICU/SCBU was not measured in either of the two included studies.

Hypoxic ischaemic encephalopathy

Hypoxic ischaemic encephalopathy was not measured in either of the two included studies.

Cost-effectiveness

Cost-effectiveness was not measured in either of the two included studies.

DISCUSSION

Summary of main results

We included two randomised trials, one parallel trial and one stepped-wedge cluster trial, involving 593,933 women, comparing track-and-trigger systems/early warning systems (TTS/EWS) and standard care. We did not identify any trials that compared TTS/EWS with an alternative TTS/EWS but will consider this comparison in future updates. The interventions evaluated in the trials were the Saving Mothers Score (SMS) and the CRADLE Vital Sign Alert (VSA) and training package. Both trials were conducted in low-resource settings. The majority of our prespecified outcomes were reported; however, for some outcomes, the Vousden 2019 study reported these as conditional outcomes only (i.e. as a cause of death or in women with the primary outcome), and we therefore did not include them in the review. The important outcomes of maternal collapse, maternal anxiety, perinatal death, hypoxic ischaemic encephalopathy and cost-effectiveness measures were not reported, although neonatal death was reported in Chakravarthy 2019.

Overall, the evidence suggests that TTS/EWS use in maternity care probably makes little to no difference in the serious outcome of maternal death. TTS/EWS may confer some benefit for a reduction in some outcomes, such as total haemorrhage and postpartum haemorrhage, but may make little to no difference in the outcomes of sepsis, eclampsia and haemolysis, elevated liver enzymes and low-platelet (HELLP) count. TTS/EWS probably makes little to no difference in maternal admission to the intensive care unit (ICU), although TTS/EWS may confer some benefit for a reduced length of maternal stay in hospital. The certainty of the majority of the evidence however is low. As such, our confidence in the effect estimates for these outcomes is limited, as further research may change the estimates.

Although neonatal death was reported in the two studies, the data from Vousden 2019 were conditional data reported in women with a primary outcome only, and we therefore excluded them from the review. The evidence on neonatal death from the Chakravarthy 2019 study suggests that TTS/EWS may have little to no difference

on neonatal death, however this evidence is based on relatively few women (n = 700) and is of low certainty.

Overall, we found minimal benefit for TTS/EWS compared to standard care for all but two of our prespecified outcomes, but equally, we found a lack of evidence of harm. Notably TTS/EWS may reduce the serious outcome of obstetric haemorrhage, including postpartum haemorrhage, and probably reduces a woman's length of hospital stay. For these reasons, TTS/EWS may have important applicability for clinical practice. The evidence, however, is currently insufficient, and consideration of other measures, such as cost-effectiveness, are required.

Of note, Vousden 2019, as part of a process evaluation of their study, explored correlations between implementation and effectiveness. These evaluations found no correlation between fidelity and effectiveness (odds ratio (OR) 0.55, 95% confidence interval (CI) 0.19 to 1.55) and no correlation between reach and effectiveness (OR 0.62, 95% CI 0.27 to 1.42). Most facilities were using the CRADLE VSA device, either alone or in combination with another device at six months, demonstrating excellent adoption, but adoption and the primary outcome were not correlated (OR 1.40, 95% CI 0.64 to 3.04). When domains were aggregated into a composite score, the combination of fidelity, reach and adoption was not associated with the primary outcome (OR 0.93, 95% CI 0.07 to 13.01).

Overall completeness and applicability of evidence

Although large numbers of women contributed to the evidence in this review, the evidence is based on two trials only, both of which were conducted in low-resource settings, and in populations of undefined risk (low- and high-risk women). While the majority of our prespecified outcomes were reported, many of these were reported in one trial only (Chakravarthy 2019), and for some outcomes in the Vousden 2019 trial, data were excluded as they were available as conditional data only. Neither of the two included studies reported on maternal collapse (cardiac or respiratory), maternal anxiety, perinatal death, length of stay in neonatal intensive care unit/special care baby unit (NICU/SCBU), hypoxic ischaemic encephalopathy or cost-effectiveness measures. Although the evidence based on the two included studies is informative and valuable for low-resource settings, the lack of trials from high-resource settings also renders the evidence incomplete, and generalising the evidence to all maternity settings is likely inappropriate. Had trials been carried out in settings with advanced speciality, multidisciplinary and technological resources, the results of the review may have been different. Future trials in these settings are required.

Certainty of the evidence

Overall, both included studies were well conducted and had either low or unclear risk of bias on all risk of bias criteria. Importantly, we assessed both studies as low risk of bias on the key elements of randomisation; that is random sequence generation and allocation concealment. We also assessed both as having low risk of bias on selective outcome reporting; however, we were unclear regarding bias related to incomplete outcome data in the Vousden 2019 study as the data for some of the outcomes was conditional only (i.e. reported in women who had another outcome).

We also had concerns regarding unclear risk of bias for the 'other bias' criterion in the Chakravarthy 2019 study. This was based on the involvement of the study PI assessing eligibility for study enrolment as well as providing care to study participants. This other bias influenced our GRADE assessments whereby we downgraded all outcomes by one level to serious based on the potential influence this other bias could have had on the results in this study (Summary of findings 1).

Although we conducted GRADE assessments for inclusion in the Summary of findings 1 on seven of our prespecified outcomes, six maternal outcomes and one neonatal outcome (neonatal death) we applied GRADE to all outcomes in the review. Downgrading was associated largely with risk of other bias for all maternal and neonatal outcomes as well as inconsistency and imprecision. Indirectness was not an issue for any of the outcomes included in our GRADE assessments.

Potential biases in the review process

At all stages of the review process we endeavoured to minimise any potential bias.

JS was a co-investigator and co-author of one of the studies included in this review (Vousden 2019). This study was independently assessed by two other review authors for inclusion and for risk of bias (VS and MN). The study's data were also extracted by two other review authors (VS and MN) and a third review author was consulted regarding data analysis issues related to this study (DD). As such, JS had no role in assessing the Vousden 2019 study for eligibility and risk of bias, or in extracting the study's data for analyses. The review authors differed minimally in the course of conducting this systematic review, and where we were uncertain we consulted members of Cochrane central team for support; for example, we consulted K Dwan as the Cochrane Methods Support unit lead and Statistical Editor for advice on meta-analysing the data from the Vousden 2019 cluster trial with data from the Chakravarthy 2019 parallel trial.

Agreements and disagreements with other studies or reviews

This is the first review that the authors' are aware of that provides an evaluation of the effectiveness of TTS/EWS for use in maternity care based on evidence from randomised trials. Earlier reviews on maternity EWS, such as those conducted to assist national clinical guideline development (NCEC/HSE 2014; DOH 2019), predate the publication of these trials; as such these guidelines are not informed by these effectiveness studies. A more recent systematic review that assessed the predictive accuracy and effectiveness of EWS in obstetrics (Umar 2019), also predates the trials included in our review; the search date of the review was to March 2018, and neither of the two trials were included. Umar 2019 includes 17 studies in their review; 11 were described as validation studies, five as effectiveness studies and one as a validation and effectiveness study. Of the six studies that were categorised as having effectiveness data, four were before-and-after studies (Austin 2014; Maguire 2015; Merriel 2016; Sheikh 2017), one was a retrospective observational study (Maguire 2016), and one was a non-randomised study which we had identified in our search but excluded as it did not meet our review's study design criterion (Shields 2016). Umar 2019 found that maternal mortality was not reduced by EWS use based on data from two studies (Shields 2016; Sheikh 2017), but severe morbidity and other clinical complications, such as postpartum haemorrhage may be reduced

with EWS, based on data from three studies (Austin 2014; Maguire 2016; Shields 2016).

Reviews on the use of TTS/EWS have also been conducted in non-maternity populations, for example in adult patients in the general ward setting (McGaughey 2007), and in paediatric populations (Lambert 2017). The McGaughey 2007 review compared outreach and EWS in a general hospital ward to a general hospital ward setting without outreach and EWS to identify deteriorating adult patients. Although no evidence for a reduction in overall mortality was found, the nature of the intervention and the population prevents comparability with the findings of our review. The review by Lambert 2017, although specific to a paediatric population, also reported mixed results for the effectiveness of EWS; in their review they state .... *"although four studies reported a significant reduction in CPA* [cardio/respiratory arrest] *and five studies found a significant reduction in mortality, there were an equal number of studies reporting non-significant findings"* (p.5).

AUTHORS' CONCLUSIONS

Implications for practice

The evidence from this review suggests that there may be some benefit of using track-and-trigger systems/early warning systems (TTS/EWS) compared to standard care in maternity care for some outcomes such as haemorrhage and maternal length of hospital stay, but currently, in low-resource settings only and in women of undefined risk. The certainty of the evidence is very low (1 outcome), low (8 outcomes) and moderate (1 outcome). For this reason, at present, caution is advised when considering the widespread clinical applicability of the review findings.

Implications for research

Based on the findings of this review, further studies are required to assess TTS/EWS use in maternity care, in particular in high-resource settings, and in groups of defined low- and high-risk women. Research is also needed that compares the effectiveness of a TTS/EWS versus an alternative TTS/EWS, and the cost-effectiveness of the systems.

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Smith 2019

Smith V, Kenny LC, Sandall J, Devane D. Physiological track-and-trigger/early warning systems for use in maternity care. *Cochrane Database of Systematic Reviews* 2019, Issue 6. [DOI: 10.1002/14651858.CD01327]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chakravarthy 2019

Study characteristics	
Methods	Parallel (1:1) RCT
Participants	**Included**: pregnant women of all ages between 6 weeks of gestation and up to 6 weeks postpartum, American Society of Anaesthesiologists Grade I-Grade IV, admitted to the obstetric wards of the study institute **Excluded**: pregnant women managed as outpatients, women admitted for termination of pregnancy, miscarriage or tubectomy, and women > 6 weeks postpartum
Interventions	**Intervention** (n = 340): the SMS developed for early identification of at-risk pregnant women based on 33 items across 3 parameters: pregnancy-related risk factors, physiological variables and biochemical tests. The physiological parameters include blood pressure, pain, temperature, pulse, respiratory rate, saturation (SpO2), urine output, and neurological status. A triple colour coding and score is assigned to each parameter. The SMS is a paper-based chart formulated based on the Modified Early Obstetric Warning Score. The chart is completed by the attending clinician on admission, and at schedules of 6, 12, 24, 36, and 48 hours. **Control** (n = 360): standard care – women were managed as per the existing hospital protocols for care.
Outcomes	• Clinical care parameters including demographic data, details of pregnancy and pregnancy-related risk factors • Mode of birth • Any morbidity in the form of obstetric haemorrhage and its complications (transfusion of blood and blood products, surgical intervention for bleeding) • Complications of hypertensive disorders of pregnancy (uncontrolled blood pressures; eclampsia; haemolysis, elevated liver enzymes, low platelets; neurological sequelae) • Sepsis • Surgical site infections • Pulmonary oedema, respiratory infections • ICU admissions • Neonatal morbidity in the form of Apgar < 6 • Neonatal ICU admissions • Any maternal or neonatal mortality • Overall hospital stay • Maternal multiple organ dysfunction and moved to ICU for further care
Notes	**Dates of study**: February 2017 to February 2018 **Funding sources**: none reported in the paper, but Clinical Trials Registry India (CTRI/2018/01/011219) indicates Niloufer Hospital for Women and Children, Osmania Medical College, Hyderabad **Declarations of interest**: no conflicts of interest declared
Risk of bias	

Chakravarthy 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation using a predetermined computer-generated simple randomisation schedule
Allocation concealment (selection bias)	Low risk	The randomisation slips were sealed in an opaque envelope and opened by a nurse not related to the study after eligibility for enrolment was confirmed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All subjects were masked to the group allocations. Although personnel implementing the intervention were unblinded, we assessed this as low risk of bias because the outcomes being measured were all objective outcome measures.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided on who precisely collected or analysed the data.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of loss to follow-up or withdrawals (confirmed by the author via email).
Selective reporting (reporting bias)	Low risk	All prespecified outcomes are reported. Numbers admitted to ICU in each group was not clear from the trial report, but were clarified by the author via email.
Other bias	Unclear risk	Page 34 states that "*It is possible that the direct involvement of the anaesthesiologist as the PI might have enhanced the care in the group where the SMS chart was applied".* The PI provided care to women attending the study site and enrolled in the trial

Vousden 2019

Study characteristics	
Methods	A pragmatic, stepped-wedge, cluster-RCT
Participants	**Included**: all women identified as pregnant or within 42 days of birth, presenting for maternity care in a cluster facility or to community healthcare providers, were exposed to the intervention.
Interventions	**Intervention** (n = 288,995): the CRADLE Vital Sign Alert (VSA) is a semi-automated device that measures blood pressure and heart rate, and calculates shock index (heart rate divided by systolic blood pressure). The device incorporates a traffic light (red, yellow green) early warning system that alerts all levels of healthcare provider to abnormalities in blood pressure and pulse secondary to obstetric haemorrhage, sepsis and pregnancy hypertension. **Control** (n = 247,238): standard care which involved various medical devices (where previously available) as used in routine maternity care with management by local guidelines.
Outcomes	**Primary outcomes** • The rate of a composite of maternal mortality or major morbidity (one of maternal death - all-cause, eclampsia or emergency hysterectomy with no double-counting per 10,000 births in each cluster each month) • Maternal death was defined as death during pregnancy or within 42 days of birth (or last contact day if contact not maintained to 42 days)

Vousden 2019 *(Continued)*

- Eclampsia was defined as occurrence of generalised convulsions with increased blood pressure during pregnancy, labour or within 42 days of birth in the absence of epilepsy or another condition predisposing to convulsions
- Emergency hysterectomy was defined as surgical removal of all or part of the uterus

Secondary outcomes

- Individual components of the primary outcome; i.e. maternal death, eclampsia or emergency hysterectomy
- ICU admission, defined as any admission to a specific ICU or an equivalent highest-level care environment within the trial area (or referral to the highest level care facility outside of the area) in areas where an ICU does not exist
- Stroke, defined as hemiparesis and/or blindness developed during pregnancy or in the 42 days postpartum lasting longer than 48 hr
- Cause of ICU admission
- Cause of maternal death
- Cause of emergency hysterectomy
- Place of eclamptic fit
- Place of maternal death
- Rate of stillbirths and neonatal deaths collected per 1000 women with a primary outcome
- Number of stillbirths (defined as born without signs of life at or after 28 weeks) per 10,000 births per month
- Number of neonatal deaths (defined as death of a live born infant after 28 weeks gestation, and within 28 days of birth) per 10,000 births per month

Notes

Number and description of clusters: 10 clusters across eight low-resource setting countries (Addis Ababa in Ethiopia, Cap Haitien in Haiti, Freetown in Sierra Leone, Harare in Zimbabwe, Gokak in India, Kampala and Mbale in Uganda, Lusaka and Ndola in Zambia, and Zomba plus the Southern Region in Malawi). Each cluster comprised at least one urban or peri-urban secondary or tertiary health facility that provides comprehensive emergency obstetric care with multiple peripheral facilities that refer to the central hospital. Facilities were identified by the local primary investigators as the main facilities that refer to the central hospital within a feasible geographical area. The 10 clusters comprised 232 primary facilities, 44 secondary facilities and 10 tertiary facilities.

Dates of study: 1 April 2016 to 30 November 2017

Funding sources: UK Medical Research Council, Indian Department of Biotechnology, and UK Department of International Development Global Research Programme (MR/N006240/1). 2 of the trial authors (JS and PTS) are supported by the UK National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital National Health Service Foundation Trust. A 3rd trial author (LCC) is supported by an NIHR Research Professorship (RP-2014-05-019).

Declarations of interest: no conflicts of interest declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomly allocated sequence run by the CRADLE statistician (PTS) determined the order in which the clusters received the intervention.
Allocation concealment (selection bias)	Low risk	All clusters were masked to the order until two months before receiving the intervention, when the next cluster to receive the intervention was informed. This 2-month lead in period was to facilitate training.

Vousden 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Because of the nature of the intervention, this trial was not masked – the outcomes are objective though, hence we assessed performance bias as low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Implementation and data collection were by the same team, introducing possible measurement bias. It is also plausible that in some clusters, use of the intervention might have resulted in increased reporting of the primary outcome if previously occurring without documentation in the community, with a bias against the intervention; although data collection was closely monitored by the local investigator and research team.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There is some loss to follow-up for perinatal outcomes although the reasons given for these are provided (end of Table 2). Furthermore, haemorrhage and sepsis are reported in the study as cause of death data only. Although not exactly missing data, it did mean that for haemorrhage and sepsis the denominator in the analyses was largely reduced as it is reflective of the numbers of women who died in the study only.
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Unclear risk	Risk of bias based on cluster design: • Recruitment bias: N/A – stepped-wedged cluster; cluster randomised and told 2 months before start of intervention. All women attending were included • Baseline imbalance: states on page e352 *"Clusters were well balanced in both groups, with no significant differences in their characteristics, including mean number of deliveries per cluster per month."* Also no differences in the characteristics of clusters (number of facilities, obstetric resources, and personnel) before and after the intervention were found. • Loss of clusters: no loss of clusters • Incorrect analysis: no • Comparability with individually randomised trials: comparable to both parallel but contamination would have been high due to training involved and device availability.

ICU: intensive care; **RCT**: randomised controlled trial; **SMS**: Saving Mothers Score

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Daly 2011	Not a randomised or quasi-randomised trial; before-and-after study
Shields 2016	Not a randomised or quasi-randomised trial; study sites volunteered as intervention or control

DATA AND ANALYSES

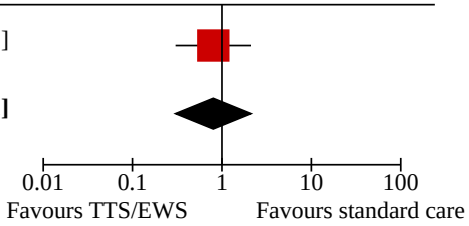
Comparison 1. Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Maternal death	1		Odds Ratio (IV, Fixed, 95% CI)	0.80 [0.30, 2.11]
1.2 Haemorrhage	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 Total haemorrhage	1	700	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.19, 0.69]
1.2.2 Antepartum haemorrhage	1	700	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.18, 3.57]
1.2.3 Postpartum haemorrhage	1	700	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.15, 0.64]
1.3 Sepsis	1	700	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.02, 1.80]
1.4 Eclampsia	2		Odds Ratio (IV, Random, 95% CI)	1.50 [0.74, 3.03]
1.5 HELLP	1	700	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.40]
1.6 Admission to ICU	2		Odds Ratio (IV, Random, 95% CI)	0.78 [0.53, 1.15]
1.7 Length of hospital stay	1	700	Mean Difference (IV, Fixed, 95% CI)	-1.21 [-1.78, -0.64]
1.8 Neonatal death	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.9 Stillbirth	1		Odds Ratio (IV, Fixed, 95% CI)	0.95 [0.87, 1.04]
1.10 Apgar score < 7 at 5 minutes of age	1	700	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.19, 1.75]
1.11 Admission to NICU	1	700	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.42, 1.11]

Analysis 1.1. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 1: Maternal death

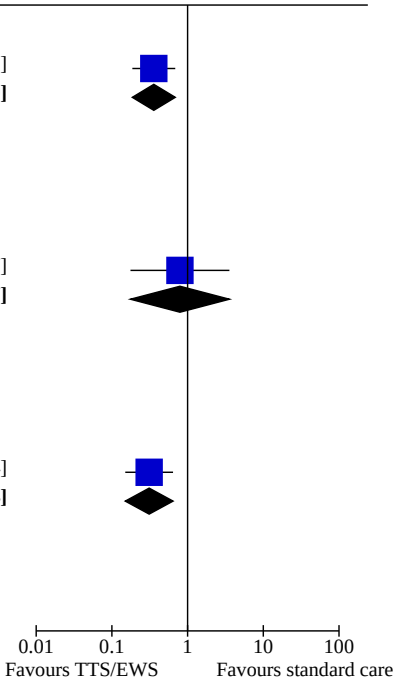
Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Vousden 2019	-0.2231	0.4951	100.0%	0.80 [0.30 , 2.11]
Total (95% CI)			**100.0%**	**0.80 [0.30 , 2.11]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



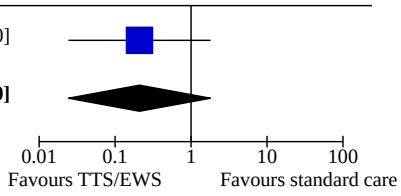
Analysis 1.2. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 2: Haemorrhage

Study or Subgroup	TTS/EWS Events	TTS/EWS Total	Standard care Events	Standard care Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Total haemorrhage						
Chakravarthy 2019	13	340	36	360	100.0%	0.36 [0.19 , 0.69]
Subtotal (95% CI)		**340**		**360**	**100.0%**	**0.36 [0.19 , 0.69]**
Total events:	13		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.09 (P = 0.002)						
1.2.2 Antepartum haemorrhage						
Chakravarthy 2019	3	340	4	360	100.0%	0.79 [0.18 , 3.57]
Subtotal (95% CI)		**340**		**360**	**100.0%**	**0.79 [0.18 , 3.57]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
1.2.3 Postpartum haemorrhage						
Chakravarthy 2019	10	340	32	360	100.0%	0.31 [0.15 , 0.64]
Subtotal (95% CI)		**340**		**360**	**100.0%**	**0.31 [0.15 , 0.64]**
Total events:	10		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.16 (P = 0.002)						



Analysis 1.3. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 3: Sepsis

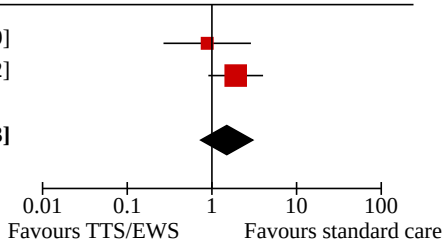
Study or Subgroup	TTS/EWS Events	TTS/EWS Total	Standard care Events	Standard care Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chakravarthy 2019	1	340	5	360	100.0%	0.21 [0.02 , 1.80]
Total (95% CI)		**340**		**360**	**100.0%**	**0.21 [0.02 , 1.80]**
Total events:	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.15)						
Test for subgroup differences: Not applicable						



Analysis 1.4. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 4: Eclampsia

Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Random, 95% CI
Chakravarthy 2019	-0.127833	0.606513	31.4%	0.88 [0.27 , 2.89]
Vousden 2019	0.647103	0.379618	68.6%	1.91 [0.91 , 4.02]
Total (95% CI)			**100.0%**	**1.50 [0.74 , 3.03]**

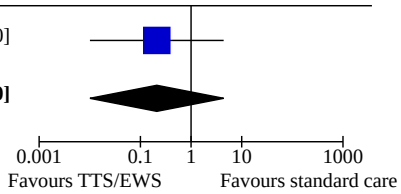
Heterogeneity: Tau² = 0.04; Chi² = 1.17, df = 1 (P = 0.28); I² = 15%
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 5: HELLP

Study or Subgroup	TTS/EWS Events	TTS/EWS Total	Standard care Events	Standard care Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chakravarthy 2019	0	340	2	360	100.0%	0.21 [0.01 , 4.40]
Total (95% CI)		**340**		**360**	**100.0%**	**0.21 [0.01 , 4.40]**
Total events:	0		2			

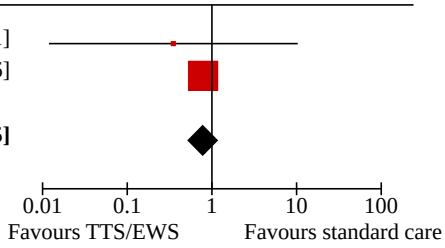
Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 6: Admission to ICU

Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Random, 95% CI
Chakravarthy 2019	-1.049822	1.725807	1.3%	0.35 [0.01 , 10.31]
Vousden 2019	-0.24	0.2	98.7%	0.79 [0.53 , 1.16]
Total (95% CI)			**100.0%**	**0.78 [0.53 , 1.15]**

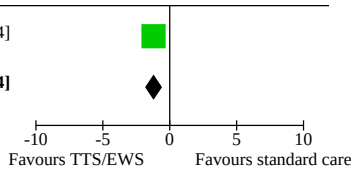
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 7: Length of hospital stay

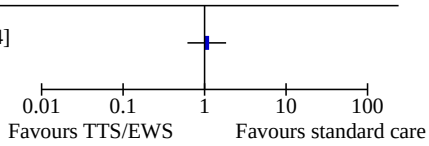
Study or Subgroup	TTS/EWS Mean	TTS/EWS SD	TTS/EWS Total	Standard care Mean	Standard care SD	Standard care Total	Weight	Mean Difference IV, Fixed, 95% CI
Chakravarthy 2019	5.75	3.71	340	6.96	4.03	360	100.0%	-1.21 [-1.78 , -0.64]
Total (95% CI)			**340**			**360**	**100.0%**	**-1.21 [-1.78 , -0.64]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.14 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 8: Neonatal death

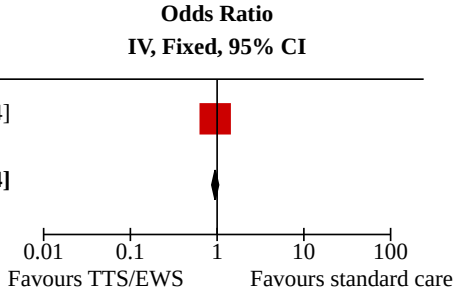
Study or Subgroup	TTS/EWS Events	TTS/EWS Total	Standard care Events	Standard care Total	Odds Ratio M-H, Fixed, 95% CI
Chakravarthy 2019	28	340	28	360	1.06 [0.62 , 1.84]



Analysis 1.9. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 9: Stillbirth

Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Vousden 2019 (1)	-0.051293	0.045532	100.0%	0.95 [0.87 , 1.04]
Total (95% CI)			**100.0%**	**0.95 [0.87 , 1.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



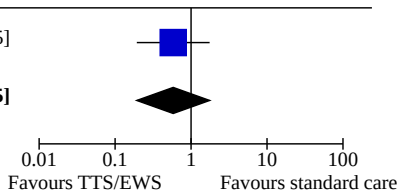
Footnotes

(1) Adjusted data; outcome measured in women with a primary outcome only (composite of maternal mortlaity and morbidity)

Analysis 1.10. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 10: Apgar score < 7 at 5 minutes of age

Study or Subgroup	TTS/EWS Events	TTS/EWS Total	Standard care Events	Standard care Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chakravarthy 2019	5	340	9	360	100.0%	0.58 [0.19 , 1.75]
Total (95% CI)		**340**		**360**	**100.0%**	**0.58 [0.19 , 1.75]**
Total events:	5		9			

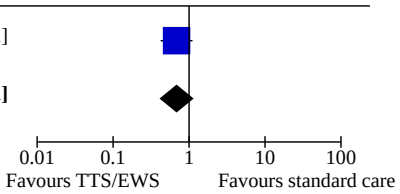
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Track-and-trigger systems/early warning systems (TTS/EWS) versus standard care, Outcome 11: Admission to NICU

Study or Subgroup	TTS/EWS Events	TTS/EWS Total	Standard care Events	Standard care Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chakravarthy 2019	31	340	46	360	100.0%	0.68 [0.42 , 1.11]
Total (95% CI)		**340**		**360**	**100.0%**	**0.68 [0.42 , 1.11]**
Total events:	31		46			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search terms for other sources

OpenGrey **database**

MEWS OR MEOWS OR MOEWS OR EWS

OR

((obstetric OR maternity OR perinatal OR pregnancy OR antenatal OR postnatal OR prenatal OR postpartum) AND ("early warning" OR "track and trigger" OR "warning system" OR "warning systems" OR "escalation policy" OR escalation policies" OR " escalation protocol" OR escalation protocols" OR "scoring tool" OR "scoring tools"))

ProQuest Dissertations and Theses

all(((obstetric OR maternity OR perinatal OR pregnancy OR antenatal OR postnatal OR prenatal OR postpartum) AND ("early warning" OR "track and trigger" OR "warning system" OR "warning systems" OR "escalation policy" OR escalation policies " OR " escalation protocol " OR escalation protocols" OR "scoring tool" OR "scoring tools"))) OR all(MEWS OR MEOWS OR MOEWS)

ClinicalTrials.gov

MEWS OR MEOWS OR MOEWS

OR

(maternity OR obstetric* OR perinatal OR pregnancy OR antenatal OR prenatal OR postpartum OR postnatal) AND ("early warning" OR "track and trigger" OR "warning score" OR "escalation policy" OR "escalation policies" OR "escalation protocol" OR "escalation protocols")

The WHO International Clinical Trials Registry Platform (ICTRP)

Each line will be run separately:

MEWS OR MEOWS OR MOEWS OR EWS

early warning AND obstetric*

early warning AND maternity

"track and trigger" AND obstetric*

"track and trigger" AND maternity

warning system* AND obstetric*

escalation polic* AND maternity

escalation protocol* AND obstetric*

escalation protocol* AND maternity

HISTORY

Protocol first published: Issue 6, 2019

CONTRIBUTIONS OF AUTHORS

V Smith drafted the review and is guarantor for the review. V Smith and M Noonan independently assessed the studies for inclusion, conducted the risk of bias assessments, extracted the relevant data, and conducted the GRADE assessments. D Devane advised on data analyses and commented on GRADE assessments. All authors reviewed and contributed intellectual content prior to submitting the review.

DECLARATIONS OF INTEREST

VS was involved in conducting a systematic literature and economic review to support the development of a National Clinical Guideline on Maternity Early Warning System (MEWS) for the Health Service Executive and the National Clinical Effectiveness Committee, Department of Health, Ireland (competitively funded; May to August 2014).

LK is Director of INFANT and has numerous grant applications under review at any given time. She has been paid by Alere to give invited symposia on a proprietary screening test for pre-eclampsia. She is the editor of Ten Teachers and has received royalties from the publishers. She is also a limited share holder in Metabolomic Diagnostics, a SME who have licensed technology that she has developed pertaining to the screening of pre-eclampsia.

JS was involved in conducting a systematic literature and economic review to support the development of a National Clinical Guideline on Maternity Early Warning System (MEWS) for the Health Service Executive and the National Clinical Effectiveness Committee, Department of Health, Ireland (competitively funded; May to August 2014). JS was also a member of the Royal College of Anaethetists (RCoA) Intercollegiate Maternal Critical Care Sub-Committee of the Obstetric Anaethetists' Association (OAA) standards development working group whose report "Enhanced care for the sick mother: standards for maternal critical care 2016" is in draft form and pending publication (www.noeccn.org.uk/resources/Documents/MCC%20NoE/MCCFinalDraft2016.pdf). JS is employed by King's College, London. NIHR CLAHRC South London: JS is supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital National Health Service (NHS) Foundation Trust. The views expressed are those of the author[s] and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. JS is a member of RCOG SANDS Stillbirth Study Group 2012-ongoing. JS was also a member of the Royal College of Anaethetists (RCoA) Intercollegiate Maternal Critical Care Sub-Committee of the Obstetric Anaethetists' Association (OAA) standards development working group whose report "Care of the critically ill woman in childbirth; enhanced maternal care" was published jointly by the RCoA, Royal College of Obstetricians and Gynaecologists, Royal College of Midwives, Intensive Care Society, Faculty of Intensive Care Medicine and Obstetric Anaesthetists'Association, in 2018. www.rcoa.ac.uk/document-store/enhanced-maternal-care-2018.

DD was involved in conducting a systematic literature and economic review to support the development of a National Clinical Guideline on Maternity Early Warning System (MEWS) for the Health Service Executive and the National Clinical Effectiveness Committee, Department of Health, Ireland (competitively funded; May to August 2014).

MN joined the review as an Evidence Synthesis Ireland (ESI) Fellow. Attendance at Cochrane training events collaboratively facilitated by Cochrane Ireland and Cochrane UK is supported under this scheme (i.e. free attendance). Expenses associated with the review (e.g. travel to mentorship meetings, travel to training events) up to EUR 1000 are also reimbursable under the ESI scheme.

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Internal sources

- Cochrane Pregnancy and Childbirth Group, UK

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Any differences between our published protocol (Smith 2019) and this full review are detailed below.

- We have added methods for assessing the trustworthiness of potential studies for inclusion in this review. These methods were developed by Cochrane Pregnancy and Childbirth.

- We had planned in our protocol to present the results for dichotomous outcomes as summary risk ratios (RRs). However, due to the inclusion of a cluster trial, we changed our summary effect measure to odds ratio (OR), as the adjusted outcome data which we needed to use in the review was reported as an OR statistic.

INDEX TERMS

Medical Subject Headings (MeSH)

Maternal Mortality; *Perinatal Death; Postpartum Period

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy