Preconception interventions to reduce the risk of alcohol-exposed pregnancies: A systematic review

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ABSTRACT

Background: The preconception period provides a unique opportunity to optimize the health of women and children. High rates of alcohol use and unintended pregnancies are common across many Western societies and alcohol exposed pregnancies (AEPs) are a possible unintended outcome. The aim of the current study was to evaluate preconception interventions for the prevention of AEPs.

Methods: A systematic search of four electronic databases (PubMed, Embase, CINAHL and PsycINFO) was undertaken for relevant peer-reviewed articles published from 1970 onwards. Studies were included if they included women and/or their support networks during the preconception period.

Results: Nineteen studies met the inclusion criteria. The majority of studies (n = 14) evaluated CHOICES-based interventions, which incorporates motivational interviewing approaches to change alcohol and/or contraceptive behavior. The five other interventions included a range of different approaches and modes of delivery. The majority of included interventions were successful in reducing AEP risk. Changes in AEP risk were more often driven through changes in contraceptive behavior, although some approaches led to changes in both alcohol and contraceptive behavior.

Conclusions: The review indicated that many interventions were efficacious at reducing AEP risk during the preconception period through preventing unplanned pregnancy. The effectiveness estimated from these clinical trials may be greater than would be seen once the interventions are implemented in practice due to lack of blinding and attrition of participants during follow-up. Further research investigating the real-world effectiveness of these intervention approaches implemented across a wide range of clinical settings would be beneficial.

Key words: health behaviors; health & lifestyle; life course; prenatal alcohol; fetal alcohol spectrum disorder

INTRODUCTION

There is growing recognition that the preconception period provides a critical opportunity in the life course to optimize the health of not only women and men, but also their future offspring (Ben-Shlomo and Kuh, 2002, Stephenson et al., 2018). Global estimates indicate that on average 44% of pregnancies were unintended in 2010-2014, with rates substantially higher in developing compared to developed countries (65% vs 45%, respectively; Bearak et al., 2018). Therefore, interventions to improve preconception health have the potential for greater impact if they also address pregnancy planning. High rates of unintended pregnancies are of particular concern in the context of high levels of alcohol consumption, which is common across many Western societies. For instance, recent research from the United States (U.S) reported that 12-month alcohol use (i.e., at least 1 standard drink; SD) and heavy episodic drinking (i.e., 4 or more SDs in a single day in the past 12 months) increased in the last 10 years in both women of reproductive age, pregnant and postpartum women (Tebeka et al., 2020). Research from the U.S also indicated that in a national population sample, 7.3% of all women of reproductive age were considered at risk of an alcohol-exposed pregnancy (AEP; Green et al., 2016).

There is increasing research attention regarding the potential negative impacts of both maternal and paternal alcohol use during the preconception period (Mullally et al., 2011, McBride and Johnson, 2016). Epigenetic changes, which are potentially reversible changes in gene expression that do not involve changes in the underlying DNA sequence, are one of the mechanisms thought to contribute to adverse outcomes (Kobor and Weinberg, 2011). Further supporting that interventions in the preconception period have a vital role to play in preventing potential adverse outcomes of alcohol use.

Previous research has documented that once women are aware of their pregnancy many will reduce or abstain from alcohol use (e.g., McCormack et al., 2017). However, given

90 many pregnancies are unplanned, alcohol exposure may occur in the period between
91 conception and pregnancy recognition (McCormack et al., 2017). A wide range of adverse
92 outcomes have been associated with prenatal alcohol exposure, including miscarriage,
93 stillbirth, low birthweight, preterm birth, and physical and neurodevelopmental impacts for
94 offspring (Mamluk et al., 2020, Bailey and Sokol, 2011). Neurodevelopmental impairments,
95 with or without specific facial features and growth deficits, in the context of prenatal alcohol
96 exposure, can result in a diagnosis of fetal alcohol spectrum disorder: a spectrum of lifelong
97 conditions (Mattson et al., 2019).

98 A significant body of research has recognized the potential for early intervention to
99 reduce the harm from alcohol on maternal and infant health among women of reproductive
100 age. A report from the World Health Organization (WHO) Regional Office for Europe
101 (Schölin, 2016) provided a rapid review of peer reviewed studies over a ten-year period
102 2005-2015, which included interventions aimed at non-pregnant and pregnant women. This
103 report concluded that preconception-focused interventions had promising results in changing
104 risky drinking and contraceptive behavior among women. Several reviews have indicated the
105 potential for reducing alcohol-related harm in pregnancy through brief interventions aimed at
106 women in general (Gebara et al. 2013) and alcohol interventions delivered to First Nations
107 populations that included women in the preconception period (Symons et al., 2018, Montag
108 et al 2012). Other reviews have looked at the potential to improve preconception care more
109 generally by addressing multiple health behaviors, including alcohol (Hemsing et al., 2017,
110 Hussein et al 2016).

111 The current review is part of a two-part series (Erng et al., 2020) that aimed to
112 summarize all the available evidence for interventions focused on prevention of AEPs. The
113 aim was to collate the evidence for interventions specifically aimed at prevention of AEPs

during the preconception period incorporating more recently published studies not included in previous reviews.

MATERIALS AND METHODS

The current systematic review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009). The study protocol was registered with PROSPERO (CRD42018107669). A large number of studies were identified, so results were separated into two reviews (Figure 1).

Search strategy

Four electronic databases (PubMed, Embase, PsycINFO and CINAHL) were searched, from 1970 to July 2018. An updated search was undertaken on 20 August 2020. Search terms included a combination of prevention-related terms (e.g., promotion, health behavior treatment, reduction); preconception/pregnancy-related terms (e.g., childbearing age, prenatal care); and prenatal alcohol exposure-related terms (e.g., FASD, AEP). See Supplementary Data File 1 for the full search strategies. The initial search, removal of duplicates and screening of titles and abstracts was performed by author MNE. Full texts were screened by authors MNE and NR and checked with authors LS and LSc. Discrepancies were resolved by discussion.

Study selection criteria

Peer-reviewed articles were eligible for inclusion if the following criteria were fulfilled: (1) the participants comprised women of reproductive age (pregnant or non-pregnant) and/or their partners and/or support networks; (2) study designs were randomized controlled trials (RCTs), controlled clinical trials, cohort studies or before-and-after studies; (3) the intervention aimed to prevent an AEP, FASD risk or incidence; and (4) quantitative outcome assessments were utilized. Outcomes of interest included: alcohol consumption (frequency/quantity); contraceptive use behavior (e.g., change in method of contraception or

frequency of use); knowledge and perception about alcohol consumption in pregnancy, neonatal outcomes (e.g., APGAR score, neurodevelopment milestones, FASD diagnoses); family wellbeing or functioning, and economic and healthcare utilization outcomes.

Studies were excluded if they were: (1) were not published in English; (2) were preclinical studies, grey literature, theses, commentaries or government reports; or (3) exclusively focused on universal primary preventive approaches, such as government initiatives on alcohol labeling, pricing, or taxation.

Study quality assessment

The methodological quality of included studies was assessed by two authors (LS and LSc) independently using a modified 27-item Downs and Black checklist (Downs and Black, 1998). Discrepancies were resolved through discussion. The checklist was used to assess the methodological quality of both randomized and nonrandomized studies, and covers four domains: (1) reporting; (2) external validity (generalizability); (3) internal validity (bias and confounding) and (4) statistical power.

Data extraction and synthesis

Data extraction was carried out by two authors (MNE and NR). Pre-developed data extraction tables were used including: author names and study country; study design and setting (i.e., community, college); sample details (i.e., sample size, gender, mean age and age range); key inclusion criteria; level of alcohol use for inclusion; duration of follow-up; intervention and control details; key measures and outcomes. A narrative synthesis was carried out addressing the key review objectives.

RESULTS

The search identified 7,471 potential articles, after duplicates were removed (Figure 1) of which 133 potentially met inclusion criteria and were retrieved for full text review. Eighty-nine articles did not meet the inclusion criteria and no full texts were found for 6 articles.

Hand searching of reference lists yielded an additional 9 relevant studies, resulting in a total of 53 eligible studies. Of these, 19 focused on women who were not pregnant (the current review) and 34 focused on pregnant or postpartum women (Erng et al., 2020). No additional studies were identified from an updated search completed prior to submission.

Study characteristics

See Table 1 for an overview of the included studies. Eighteen studies were undertaken in the U.S and one in South Africa (Rendall-Mkosi et al., 2013). The majority of studies were RCTs (n = 12), followed by before-and-after studies (n = 6) and one study had a descriptive longitudinal design (Hanson et al., 2013). Three studies recruited women from community-based clinics (Walker et al., 2005, Ingersoll et al., 2013, Delrahim-Howlett et al., 2011); three from primary care clinics (Velasquez et al., 2017, Rendall-Mkosi et al., 2013, Manwell et al., 2000); three from American Indian/Alaska Native communities (Montag et al., 2015b, Hanson et al., 2013, Hanson et al., 2017); two from colleges (Ingersoll et al., 2005, Ceperich and Ingersoll, 2011); three were delivered across multiple settings – see Table 1 for the specific details (Wilton et al., 2013, Floyd et al., 2007, Project CHOICES Intervention Research Group, 2003), two utilized online recruitment methods (e.g., craigslist) (Farrell-Carnahan et al., 2013, Ingersoll et al., 2018), one utilized online and local media advertisements (Tenkku et al., 2011), one utilized sexually transmitted disease (STD) clinics (Hutton et al., 2014) and one implemented local media advertisements (Sobell et al., 2017). The majority of studies (n = 16) included women who were specifically at risk of an AEP. The two components of the inclusion criteria for AEP risk were (1) sexual activity/contraceptive use; and (2) alcohol use behavior (see Supplemental Data File 2 for a comprehensive summary of the inclusion criteria regarding AEP risk). Manwell et al. (2000) included women of childbearing age who were drinking at risky levels and Montag et al. (2015b) included women who were able to become pregnant with no other criteria stated.

Lastly, Walker et al. (2005) included women who were requesting pregnancy tests and/or emergency contraception.

Intervention characteristics. Most of the included studies (*n*=14) were based on CHOICES, an intervention including motivational interviewing (MI) focusing on changing alcohol use and/or contraception use behaviour (Table 2). The original CHOICES intervention, which included four MI sessions focused on alcohol use behavior and one contraceptive counselling session, was evaluated in three studies (Velasquez et al., 2017, Floyd et al., 2007, Project CHOICES Intervention Research Group, 2003). Rendall-Mkosi et al. (2013) also delivered a five-session CHOICES-based program, but with the contraceptive counselling integrated into each session. Hanson et al. (2013; 2017) adapted the four-session CHOICES to First Nations communities, though in two out of three sites Hanson et al. (2017) delivered a two-session intervention. Velasquez et al. (2017) implemented a three-session CHOICES approach, which also included a focus on tobacco. Wilton et al. (2013) utilized a two-session model that also integrated cognitive behavioral therapy (CBT) techniques and Ceperich and Ingersoll (2011), Ingersoll et al. (2005) and Ingersoll et al. (2013) tested single session versions of the CHOICES approach (i.e., referred to as BALANCE and EARLY interventions).

Different modes of delivery were used in a number of CHOICES studies, including phone-and/or mail-based adaptations (Hanson et al., 2013, Wilton et al., 2013, Farrell-Carnahan et al., 2013, Sobell et al., 2017), and an online intervention, including six fully automated web-based sessions designed to match the MI processes involved in CHOICES sessions (Ingersoll et al., 2018). Hutton et al. (2014) implemented CHOICES in STD clinics and following an initial face-to-face session provided the option of follow-up sessions via phone. There were five non-CHOICES interventions; two (Delrahim-Howlett et al., 2011, Montag et al., 2015b) were single session web-based interventions adapted from e-

CheckUpToGo, one of which was delivered in First Nations communities (Montag et al., 2015b). Manwell et al. (2000) tested Project TrEAT, which included two physician visits and two phone calls from a nurse designed to reduce alcohol use. Tenkku et al. (2011) examined a mail and web-based self-guided change intervention that included four modules that included individualized motivational content. Lastly, Walker et al. (2005) examined the effectiveness of an educational brochure about FASD to increase knowledge for women presenting for emergency contraception and/or pregnancy tests.

Control characteristics. Twelve studies included control groups. The majority (n = 7) utilized an information brochure or booklet on general health or risks associated with alcohol use as the control condition. In other studies, the control groups were information video and information brochure (Ingersoll et al., 2013), assessment and treatment as usual (Montag et al. (2015b), and brief advice and referral to community services (Velasquez et al. (2017). Two studies used the same intervention but delivered over the phone (Wilton et al. (2013) or as a web-based model (albeit without the interactive responses tailored to the individual) (Ingersoll et al. 2018).

Quality of methodological reporting

Table 3 provides a summary of reporting for the included studies. The domains with consistently higher ratings were reporting quality and internal validity. None of the included studies included reporting in relation to the presence or absence of unintended outcomes of the interventions being evaluated. Within the internal validity domain, weaker elements were lack of blinding of participants or outcome assessors and lack of clarity on participant's adherence with the assigned intervention. Domains with consistently lower ratings were external validity and sample size and power.

Study outcomes

Multi-session study outcomes – face-to-face. Six studies tested multi-session CHOICES delivered face-to-face, all reported significant reductions in AEP risk (Table 2). For three studies this was achieved through significant reductions in both alcohol and contraceptive use behaviors (Project CHOICES Intervention Research Group, 2003, Floyd et al., 2007, Velasquez et al., 2017), and for the remaining two studies predominately through changes in contraceptive use behavior, with smaller reductions in alcohol use reported (Rendall-Mkosi et al., 2013, Hanson et al., 2017). Hutton et al. (2014) undertook a pragmatic real-world evaluation of the CHOICES intervention across two STD clinics. At 6-months, slightly more women at the Denver site reported changing both alcohol and contraceptive behaviors (24%), compared to alcohol (19%) or contraceptive behavior (19%) alone. Whereas at the Baltimore site, more women reported changing contraceptive behavior alone (37%) compared to both behaviors (25%). Lastly, Manwell et al. (2000) undertook an RCT comparing a brief alcohol treatment (Project TrEAT) to an information only control. This was a mixed delivery model, which included two face-to-face physician appointments and two follow-up phone calls provided by nurses two weeks after each face-to-face appointment. Significant reductions in the number of drinks in the past 7 days and number of binge drinking episodes in the past 30 days were reported for the treatment group compared to control.

Multi-session study outcomes –phone-based. Two studies examined multi-session phone-based interventions. Wilton et al. (2013) found a significant reduction in AEP risk (100% to 29%), risky alcohol use (100% to 84%), and increased effective contraceptive practices (0% to 64%), across both groups with no significant differences between the groups. Again, larger changes in contraceptive use behavior were reported, compared to alcohol use behavior. The authors concluded that telephone-based brief intervention may be just as effective as face-to-face intervention. Hanson et al. (2013) showed significant

reduction in AEP risk between baseline (54%) and all other visits, with no significant differences between, 3 (29%), 6 (27%), 9 (35%) and 12 months (20%). There was a significant reduction in alcohol use behavior across all measures (i.e., average drinks per day, average drinks per week, most drinks and times that had 3+ drinks) with each additional follow-up assessment and a significant reduction in ineffective contraception use in the first 3-months (29% to 10%), but then this remained constant for the subsequent follow-up assessments.

Multi-session study outcomes – web-based. Two studies were identified that provided multi-session, web-based interventions. In Ingersoll et al. (2018), 72% of participants completed all six components of the intervention, which was deemed as feasible and acceptable. Significant differences between the treatment and control groups were reported for contraceptive use behavior at 6 months (39.39% vs. 16.13% respectively), whereas both groups reported similar reductions in risky drinking at 6 months (18.18% vs. 19.36%). Overall, at 6 months AEP risk was significantly reduced in the intervention group (36.7%), but not in the control group (16.13%). Additionally, Tenkku et al. (2011) showed reductions in AEP risk; 70.6% in the mail-based group and 56.7% in the web-based group were no longer at risk at 4-month follow-up. An equal proportion of women in the mail-based intervention (22%) and the web-based intervention (23.1%) reported they had quit drinking. Similarly, effective contraception use was reported by 50.8% of the mail-based group and 41.2% of the web-based group (41.2%) at 4 months follow-up.

Single-session study outcomes – face-to-face. Four studies were included that examined single-session face-to-face intervention models. Ingersoll et al. (2005) found that at 1-month follow-up, more women in the treatment group (BALANCE intervention) compared to women in the control had reduced their AEP risk (73.9% vs 54.3%, respectively). Risk reductions related to both behaviors, however women demonstrated greater change in

contraception behavior than in drinking behavior. This was even more pronounced at the 4-month follow-up undertaken by Ceperich and Ingersoll (2011), with the full sample where significant reductions were still found in AEP risk in the intervention (79.8%) compared to the control group (65.1%), with non-significant differences in effective contraceptive use (68.7% and 55.1%, respectively), and reductions in risky drinking (33.7% and 22.4%, respectively).

Ingersoll et al. (2013) indicated that at 6 months, fewer intervention participants (EARLY intervention) were at risk of an AEP (44.9%) compared to those in the informational video (63.8%) or informational brochure (54%) groups. The differences were due to contraceptive use, but not for alcohol use. The authors also compared their results with previous CHOICES and BALANCE interventions and found that the risk reductions were smaller than those achieved in the earlier interventions. Lastly, Walker et al. (2005) found that an educational FASD brochure resulted in more women presenting for emergency contraception and/or pregnancy tests.

Single-session study outcomes – mail/phone. Two studies tested single-session mail and/or phone-based interventions. Farrell-Carnahan et al. (2013) found that participants reported strong levels of therapeutic alliance and treatment credibility of the EARLY Remote intervention, delivered over mail or phone. Significant reductions were found at 6-month follow-up for AEP risk (68.8%), risky drinking (87.5%) and ineffective contraception (75%). The authors concluded that in comparison to results from Ingersoll et al. (2013), EARLY Remote may be slightly less effective than the face-to-face version. Sobell et al. (2017) found no differences in AEP risk at follow-up between intervention and control group, though there was a significant difference between students and non-students, as the former were more likely to take up effective contraception.

Single-session study outcomes – web-based. Two studies examined adapted versions of e-CheckUpToGo a single-session intervention focused solely on alcohol. Delrahim-Howlett et al. (2011) delivered the intervention in Women Infant and Children Clinics and found no significant difference between intervention and control group. Similarly, Montag et al. (2015) found that both intervention and control groups experienced reductions in alcohol consumption, with no differences between groups. Both studies concluded that rigorous, comprehensive assessment alone, even without an intervention, may be sufficient in some circumstances to reduce risky drinking and AEP risk.

DISCUSSION

This systematic review has provided a detailed summary of the available evidence regarding interventions during the preconception period to prevent AEPs. Overall, the majority of studies included in the review found significant reductions in AEP risk over 1 to 12-month follow-up periods. Intervention efficacy was generally driven by changes in contraceptive behavior, thus preventing unplanned pregnancy, with some reductions also found in alcohol consumption. While reductions in alcohol use were noted, many women were consuming alcohol at risky levels and even when reductions in alcohol use were found, drinking was still higher than recommended levels. Generally, multi-session interventions reported greater reductions in AEP risk. However, it was notable that changes in behavior were also found following less intensive (i.e., single session interventions), including where comprehensive assessment only led to reductions in alcohol use (Montag et al., 2015b). It is important to note that the interventions aimed to reduce drinking to thresholds consistent with low-risk recommendations for non-pregnant women and not abstinence, which is the recommendation for women planning a pregnancy. From the findings of the included studies, it is unclear the impact an intervention may have on alcohol use behavior once women ceased contraception and/or were planning a pregnancy.

The results of the current review also need to be interpreted in the context of the quality appraisal results. Lack of blinding and self-reported subjective outcome measures could lead to over-estimation of the treatment effects (Higgins et al., 2019). Many of the included studies experienced considerable loss to follow-up, a source of bias that could also skew findings towards an over-estimation of benefit. Furthermore, most studies scored poorly on external validity, meaning representativeness of recruited participants in relation to the overall population, as well as the type of intervention and delivery being representative of usual treatment women might receive. No studies reported on the presence or absence of unintended outcomes of interventions (e.g., experiences of domestic or family violence related to reduction or abstinence of alcohol and/or other substances) and limited information was provided about women's views on receiving the intervention, which may be important in the context of drop-out rates. Devine and Barnhill (2018) noted that for weight-loss interventions, a lack of evaluation of adverse outcomes may result in lack of effects for specific sub-groups. Further research should therefore also explore these issues for AEP prevention approaches and whether unintended effects may be associated with non-compliance with the intervention or withdrawal from the study.

Considerations for future research and practice

While the results of the current review were promising, it is problematic that limited research to date has been undertaken in real-world settings. Implementation-focused research is required to consider what works for which women, in what settings, and what contextual factors should be addressed (e.g., intimate partner violence, mental health, other substance use, nutrition). Additionally, in the majority of the included studies trained research staff provided the interventions, therefore, considerations regarding the type of practitioners, amount of training and ongoing supervision and funding required for implementation and maintenance are important areas for future research and practice. Implementation-focused

research is particularly important given the complexities of delivering preconception care in many health systems. The WHO published a global consensus in 2013 on preconception care and a number of countries, such as the U.S, Netherlands and Italy have national guidelines. However, many countries, including Canada and Australia do not have national guidelines. More widespread development and utilization of clinical practice guidelines regarding preconception care may encourage funding and implementation of evidence-based AEP prevention approaches. Additionally, future research and practice could explore the possibilities of providing pre-conception focused care across a wide range of settings, this could include primary care, sexual health clinics, domestic violence services and specialist alcohol and other drug services. Research could also investigate if there could be benefits of targeted messaging through social media and online blogs, which can be primary sources of information for women of reproductive age (Harding, Whittingham and McGannon, 2021) and could thus, provide opportunities to access a wider audience for dissemination of prevention messages.

The current review did not identify any interventions that included consideration of a woman's partner or wider social context (e.g., family members or friends) as a part of the intervention. This is also consistent with the recent review of pregnancy interventions (Erng et al., 2020), which also noted limited focus on wider contextual factors, which may maintain alcohol use and in this case, may contribute to contraceptive decision making. For instance, Montag et al. (2019) found that alcohol use in women of reproductive age within a Southern California American Indian community was strongly influenced by female friends and relatives. Deutsch (2019) using data (n = 2,097) from the U.S National Longitudinal Study of Adolescent to Adult Health highlighted that women who had experienced intimate partner violence reported higher levels of alcohol use, lower birth control use and were at increased risk of an AEP. Only one intervention study was identified that included a dual focus on

preventing tobacco exposed pregnancies (Velasquez et al., 2017). Given the wide range of maternal factors associated with increased risk of FASD (e.g., nutrition, polysubstance use, psychological distress, having partners/family members who are heavy drinkers; May & Gossage, 2011) incorporating a more holistic approach to prevention could be beneficial. Screening that considers a range of associated AEP risk factors and stepped care models, where those who do not respond to a single session could be referred for more individualised support could be effective in providing services and allocating resources effectively. Future research could consider testing approaches through sequential multiple assignment randomised trials (SMART) study designs (Wallace et al., 2016), which are adaptive trial designs whereby dosage, type, or delivery mode of an intervention could be adjusted in order to meet the unique and changing needs of an individual.

There may be particular sub-groups of women, based on their contraceptive use behaviour for whom interventions may be more or less effective. For example, a recent large (n = 4,952) longitudinal study of women's health found that women not using contraception had higher odds of being overweight/obese, were previous or current smokers, consumers of alcohol, reported fair or poor general health and very high levels of psychological distress (Rowlands et al., 2020). The importance of considering mental health was also highlighted in three studies that undertook secondary analyses of included interventions (Montag et al., 2015a, Penberthy et al., 2014, Johnson et al., 2017). Montag et al. and Johnson et al. both found depression was associated with increased alcohol use. In Johnson et al. (2017) women experiencing depression reported more reasons against changing alcohol use (i.e., increased number of cons vs pros for changing behaviour) and higher levels of temptation to drink. While Montag et al. (2015a) found women who were experiencing depression decreased alcohol use in response to intervention to a greater extent than women not experiencing depression. Further to this, Penberthy et al. reported that women who reported higher

412 depressive symptomology experienced greater risk reductions in the MI plus feedback
413 condition (i.e., EARLY) compared to the other types of interventions provided (i.e., video
414 information or an informational brochures). Therefore, available evidence highlights the
415 importance of screening for depressive symptomology and tailoring intervention delivery to
416 maximise benefits.

417 In addition to a shift to implementation focused approaches within AEP prevention,
418 there remains a need to be fully inclusive when designing AEP prevention studies. In
419 particular, marginalized communities of people, for instance people from First Nations and
420 LGBTQIA communities have specific needs surrounding any public health program and their
421 voices must be included when developing such projects. A participatory approach to
422 understanding reasons for drinking (e.g., Shrestha, Weber, Ingersoll, and Hanson, 2018), as
423 well as barriers to accessing safe and affordable contraception is an important next step in
424 designing and implementing interventions in partnership with marginalized communities.

425 The outcome measures for most studies focused on contraceptive and alcohol use, but
426 studies exploring outcomes for women who conceived and the subsequent longer-term
427 outcomes for infants and children are needed to establish the potential to prevent harm due to
428 alcohol exposure. However, this would require more resource-intensive studies. Although if
429 interventions have an impact on multiple behaviours and outcomes in the longer term, there
430 may be more incentive to invest in these types of interventions. Notably, studies included in
431 the current review indicated that remotely delivered interventions, such as mail-based or web-
432 based (Tenkku et al., 2011) and phone (Wilton et al., 2013) appeared to have similar effects
433 to interventions delivered face-to-face. While additional research is needed to further
434 examine these approaches, current results highlight the potential for phone, mail or web-
435 based interventions to improve outcomes. This is a critical time for advancing remotely
436 delivered interventions in the context of the COVID-19 pandemic. Technology-based

intervention delivery could also increase engagement given this is still a stigmatized health issue and could be particularly beneficial for women living in rural/remote areas (Hai, Hammock & Velasquez, 2019).

Lastly, the majority of interventions to date have been developed and implemented in the U.S. However, Popova and colleagues (2017) reported the five countries (i.e., Russia, Denmark, Belarus and Ireland) with the highest estimated prevalence of prenatal alcohol use were all from the European region. Consequently, much of the available research literature to date has limited consideration of cultural factors that could influence intervention effectiveness. This could include attitudes and accessibility of contraception and differences in health systems, which may require specific design considerations or adaptations. A secondary data analysis undertaken by Letourneau et al. (2017) examined differences between women who requested Project Healthy Choices (Sobell et al., 2017) mail-based intervention materials in English or Spanish, with the former reporting higher rates of reduced risk outcomes. Future research incorporating people from a wider range of culturally and linguistically diverse backgrounds, particularly in countries where there is a high prevalence of alcohol use would be timely and beneficial.

Strengths and Limitations

The current review adhered to a registered protocol and included multiple reviewers in the data extraction and quality appraisal process. However, there are a number of limitations that need to be taken into consideration when interpreting the current results. Unpublished reports, foreign language studies and interventions focused on universal prevention approaches were excluded, which may have limited the identification of potential intervention approaches. The reliance on peer-reviewed literature may mean that we have omitted more real-world research and thus, have not accurately captured what is currently implemented in practice. Furthermore, the current review also relies on the information that is

reported in the available publications. For instance, given journal word count limitations there may be important contextual factors or implementation strategies that were not reported, which could be beneficial in interpreting the effectiveness of particular interventions and informing future research and clinical practice. This also applies to the quality of reporting, as this also relies on information reported in the included studies. For instance, additional studies published on the same intervention where more details may be available were not included. Additionally, although specific study details may have been reported to independent ethics review boards (e.g., adverse events) this could not be assessed unless it was overtly stated in the included study. There other limitations noted in applying the quality appraisal tool. For example, although the tool was designed and selected based on the fact that it could be used to appraise different types of study designs, a number of questions included in the tool are particularly focused on studies that included control groups and was therefore, not a good fit for before-and-after study designs. Future research could consider applying distinct appraisal tools for each type of study design.

Conclusion

This is a vital research and service delivery area to support women's and child health. The current review provides an up-to-date summary of the available evidence regarding the efficacy of preconception interventions. Overall results demonstrated reductions in AEP risk through prevention of unplanned pregnancy and, to a lesser extent, reductions in alcohol use. Although there is a growing body of efficacy research it is critical future research investigates the application of these interventions in real world settings where a variety of critical implementation factors can be considered and in countries other than the U.S, particularly those with high prevalence of prenatal alcohol exposure.

Our findings indicate that screening to identify vulnerable women for implementation of targeted interventions may enhance impact. For example, empowering women in the

control of their fertility through contraception focused interventions, and screening for depression or psychological distress to identify women who might benefit from more intensive intervention. It is encouraging that remote interventions have demonstrated efficacy as this may expand options for resource limited, pandemic influenced, and rural communities. In addition, results support encouraging future studies to minimize loss to follow-up and to follow women through any subsequent pregnancies to evaluate pregnancy outcomes. To facilitate future evaluations and to limit inevitable misclassification of studies due to inadequate published descriptions of studies, journal editors and authors may be prompted to ensure evaluation parameters are addressed in manuscripts submitted for publication. Given the huge and costly impact of AEPs, a greater emphasis on preconception interventions is called for. Although there is a growing body of efficacy research, the effects of interventions on the health of women, actual pregnancy rates, and outcomes of pregnancies, including infant and child health, are currently unknown. It is critical that future studies address these questions.

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693

694 **Table 1.** Study characteristics
695

Authors (Year) Country	Study design and setting	Analyzed sample size Gender; M_{age} (Range)	Key inclusion criteria	Level of PAE for inclusion	Longest follow-up period
Ceperich et al. (2011)[a] U.S.	RCT College	*N* = 207 T *n* =101, C *n* =106 Female; M_{age} T=20.19yrs C=21yrs (18-24 yrs)	Sexually active and ineffective contraception use.	Current risky alcohol consumption[b]	4 months
Delrahim-Howlett et al. (2011) U.S.	RCT Women, Infant and Children Clinics Web-based	*N* = 117 T *n* = 60 C *n*= 57 Female; M_{age} T=26.91yrs C=25.75yrs; (18-45yrs)	Sexually active and capable of future pregnancy.	Current risky alcohol consumption[c]	2 months
Farrell-Carnahan et al. (2013) U.S.	BAA Remote community Mail/phone-based	Treatment *N* = 35 Female; M_{age} 27.3yrs (18-44yrs)	Sexually active, able to fall pregnant and at risk for AEP[d]	Current risky alcohol consumption[e]	6 months
Floyd et al. (2007) U.S.	RCT Multi-site[h]	*N* =593 T *n* = 291 C *n* = 302 Female; M_{age} T=29.8yrs, C= 29.45yrs (18-44yrs)	Sexually active, able to fall pregnant, without effective contraception, not pregnant or planning	Current risky alcohol consumption[i]	9 months
Hanson et al. (2013) U.S.	Descriptive longitudinal American Indian communities	*n* = 51 drinking analysis; *n* = 30 contraception analysis[j] Female; M_{age} *NR* (18 – 44yrs)	Sexually active, able to fall pregnant/not using IUD or Depo, not trying to conceive	Any level in the past 3 months	12 months
Hanson et al. (2017) U.S.	BAA 2 American Indian reservation sites and 1 urban site	Treatment *N* = 99 Female; M_{age} 29yrs (18-46yrs)	Sexually active, able to fall pregnant, not or incorrectly/inconsistently using contraception	Exceeded low risk[k]	6 months
Hutton et al. (2014) U.S	BAA 2 STD clinics (Baltimore & Denver)	Baltimore *N* = 97 Denver *N* = 74 Female; demographics varied by site[l]	18-44 yrs, able to become pregnant, agreed to participate	Heavy alcohol use exact amount not defined	6 months

Ingersoll et al. (2005) U.S.	RCT College	*N* = 199 Treat *n* = 94 Control *n* = 105 Female; M_{age} 20yrs (18 – 24yrs)	At risk for an AEP[m]	Current risky alcohol consumption[n]	1 month
Ingersoll et al. (2013) U.S.	RCT Community	*N* = 59 Treat n = 49 Control 1 *n* = 63 Control 2 *n* = 47[0] Female; M_{age} 27.9yrs; (18-44yrs)	Sexually active, at risk for an AEP[p] and able to fall pregnant	Current risky alcohol consumption[q]	6 months
Ingersoll et al. (2018) U.S.	RCT Web-based Online recruitment	*N* = 64 Treat *n* = 33 Control *n* = 31 Female; M_{age} 28yrs (18 – 44yrs)	Able to fall pregnant, and ineffective, inconsistent or absent contraception past 3 months	Current risky alcohol consumption[r]	6 months
Manwell et al. (2000) U.S.	RCT Primary care clinics	*N* = 174 Treat *n* = 83 Control *n* = 91 Female; M_{age} *NR* (18-40yrs)	Women aged 18 - 40 no other criteria stated	Problem drinkers[s]	48 months
Montag et al. (2015b) U.S.	RCT Web-based Recruited from AIAN health clinics	*N* = 242 Treat *n* = 111 Control *n* = 131 Female; M_{age} 28.6yrs (18-45yrs)	Women aged 18 – 45 years of childbearing potential Native American	No criteria	6 months
Project CHOICES Research Group (2003) U.S.	BAA Multi-site[f]	Treat *N* =143 Female; M_{age} 30.87yrs (18-44yrs)	Sexually active, able to fall pregnant, ineffective or no contraception, not pregnant or planning	Current risky alcohol consumption[g]	6 months
Rendall-Mkosi et al. (2012) South Africa	RCT Primary care clinics	*N* = 125 Treat *n* = 61 Control *n* = 64 Female; M_{age} 29.8yrs (18-44yrs)	Not pregnant, ineffective contraception, able to fall pregnant and sexually active	Current risky alcohol consumption[t]	12 months
Sobell et al. (2017) U.S.	RCT Mail-based	*N* = 325 Treat *n* = 164 Control *n* = 161 Female; M_{age} 25.9yrs (18-44yrs)	Sexually active, ineffective contraception	Current risky alcohol consumption[u]	6 months

	Recruited through local advertisements				
Tenkku et al. (2011) U.S.	BAA Web- and mail-based Recruited through online and local advertisements.	*N* = 319 web *n* = 260 mail *n* = 59 Female; M_{age} *NR* (18-44yrs)	Sexually active, able to become pregnant, no or ineffective contraception	Any level in the past 30 days	4 months
Velasquez et al. (2017) U.S.	RCT Primary care clinics	*N* = 248 Treat *n* = 126 Control *n* = 122 Female; M_{age} 31yrs (18-44yrs)	Sexually active, able to become pregnant, not pregnant or planning, not using effective contraception	Current risky alcohol consumption[v]	9 months
Walker et al. (2005) U.S.	BAA Community clinics[w]	Treatment *N* = 50 Female; M_{age} 23.8yrs (18 – 48yrs)	Women requesting pregnancy tests and/or emergency contraception	No criteria	Immediately
Wilton et al. (2013) U.S.	RCT Multisite [x]	*N* = 89 Female; M_{age} 25.5yrs (18-44yrs)	Sexually active, not using effective contraception and not pregnant.	Current risky alcohol consumption[y]	6 months

Note. RCT = randomized controlled trial; T = treatment; C = control; BAA = before and after; M = mean; yrs = years; AEP = alcohol-exposed pregnancy; NR = not reported; STD = sexually transmitted disease; AIAN = American Indian and Alaska Native;

[a] 4-month follow-up of Ingersoll et al. (2005)

[b] ≥ 4 standard drinks per occasion at least once in the past 90 days or consumed ≥ 7 standard drinks per week.

[c] ≥ 3 drinks on at least 1 occasion in the previous month

[d] Current risky drinking and no or unreliable contraception paired with vaginal intercourse during the past 90 days

[e] > 7 standard drinks per week on average and/or > 3 standard drinks on at least one occasion in the past 90 days

[f] 6 community-based settings in 3 large cities: primary care practice, media, large urban jail, 2 drug and alcohol treatment centres, hospital-based obstetrics and gynaecology practice and community-based primary care centre.

[g] > 7 standard drinks/week or ≥ 1 binge drinking episode (≥ 5 standard drinks /day) during past 3 months.

[h] 6 community-based settings in 3 large cities: primary care practice, media, large urban jail, 2 drugs and alcohol treatment centres, hospital-based obstetrics and gynaecology practice and community-based primary care centre

[i] ≥ 5 or more standard drinks in a day (binge drinking)

[j] *n* at the longest follow-up period – 12 months

[k] binge drinking – 4 or more drinks per occasion or 8 or more drinks per week

[l] Baltimore 55% ≥ 25 yrs and largely African American (87%); Denver 51% 18-24 yrs and primarily white (62%), with 41% Hispanic.
[m] Having sexual intercourse with a man in the past 90 days, using ineffective/no contraception
[n] ≥ 5 or more standard drinks per occasion (binge) at least once in the past 90 days or ≥ 8 standard drinks per week on average.
[o] Control group 1 = informational brochure condition; control group 2 = information video condition
[p] at least one unprotected episode of vaginal sex with a male partner and drinking at risky levels
[q] > 3 standard drinks on one occasion or > an average of 7 drinks per week
[r] 1 episode of ≥ 4 standard drinks per day (considered a binge) during the past 3 months
[s] > 11 standard drinks per week (132 g), > 4 standard drinks per occasion or two or more positive responses to the CAGE questions.
[t] Over the past 3 months > 5 drinks at one sitting in the past 3 months or > 7 drinks per week
[u] Consumed on average ≥ 8 standard drinks per week and/or engaged in binge drinking (≥ standard drinks on 1 occasion)
[v] In the previous 3 months > 3 drinks per day or > 7 drinks per week, on average
[w] One was a university health service, second was a family practice centre
[x] Public health and family practice clinics, college campuses and a community women's expo
[y] > 7 drinks per week or > 3 drinks in any one day during the past 90 days

750 **Table 2.** Intervention and control details, key outcomes and findings

Study	Intervention	Control	Key outcomes	Key Findings
Ceperich & Ingersoll (2011)	BALANCE: single 60 -75 minute face-to-face BI session and personalized feedback.	Informational pamphlet about women's health	• AEP risk • TLFB alcohol and contraceptive use	• Significant ↓ AEP risk in intervention (79.8% no longer at risk) vs. control (65.1%; p =0.02). • Non-significant trends for maintained changes in either risk behavior at 4-months. • Greater proportion changed contraceptive compared to drinking behavior.
Delrahim-Howlett et al. (2011)	Adapted e-CHUG: web-based alcohol use assessment and personalized feedback.	Information on risks associated with general alcohol use and during pregnancy.	• Risky drinking TLFB & T-ACE	• Reduction in risk drinking occasions for both intervention (72%) and control (68%; OR=1.20; p=0.634).
Farrell-Carnahan et al. (2013)	EARLY-Remote: mailed package that included personalized feedback followed by one 60-minute MI based telephone call	No control	• AEP risk • TLFB: Alcohol and contraceptive use	• Significant ↓ AEP risk from baseline (100% at risk) to 6-months (68.8% at risk). • Significant ↓ risky drinking from baseline (100%) to 6-months (87.5%). • Significant ↓ ineffective contraception from baseline (100%) to 75% at 6 months.
Floyd et al. (2007)	CHOICES: 4 face-to-face MI sessions +1 contraceptive counselling session.	Information only	• AEP risk • TLFB: daily drinking, sexual activity and contraceptive use	• Significant ↓ AEP risk in intervention (69.1%) vs. control (54.3%) at 9-months. • Intervention group more likely to reduce alcohol below risky levels (OR=2.5) and use effective contraception (OR=2.4) compared to controls.
Hanson et al. (2013)	Phone-based-CHOICES: mailed package that included personalized feedback + 4 follow-up MI informed phone calls.	No control	• AEP risk • Alcohol use[a] • Contraceptive use[a]	• Significant ↓ AEP risk between baseline (54%) and all other visits. No differences between 3, 6, 9 and 12 months (20% at risk). • Significant ↓ in alcohol use across all measures with each follow-up session. • Proportion not using contraception ↓ in the first 3 months (29 to 10%) then remained constant.

Study	Intervention	Control	Key outcomes	Key Findings
Hanson et al. (2017)	Oglala Sioux Tribe CHOICES: 1 site provided 4 MI sessions and 2 sites provided 2 MI sessions. Modified CHOICES content based on community input. Face-to-face.	No control	• AEP risk • Daily diaries: alcohol and contraceptive use and sexual activity.	• Significant ↓ in proportion at risk for an AEP from baseline to 6 months (18.1 to 66.3).[b] • Most participants ↓ AEP risk through effective contraception (61.5% at 6 mths). • Some participants changed both contraception and alcohol use (18.5% at 6 mths).
Hutton et al. (2014)	Modified CHOICES varied session lengths from 1 to 5 sessions.	No control	• AEP risk • Alcohol use • Contraceptive use	• Baltimore: 83% ↓ AEP risk, 18% ↓ alcohol only, 37% changed contraception only, 25% changed both behaviours at 6 months. • Denver: 62% ↓ AEP risk, 19% ↓ alcohol only, 19% changed contraception only, 24% changed both behaviours at 6 months.
Ingersoll et. al. (2005)	BALANCE: single 60-to 75-min face-to-face personalized feedback and MI-based counseling session.	Information pamphlet on women's health	• AEP risk • TLFB: alcohol and contraceptive use	• Significant ↓ AEP risk in intervention (73.9%) vs control (54.3%; $p = 0.005$) at 1-month • 25% of intervention group reported no risk. drinking vs 15% in the control group (p=0.02) • 64% of intervention group reported effective. contraception vs. 48% of control group (p=0.03).
Ingersoll et al. (2013)	EARLY: Single 60-min face-to-face MI plus assessment feedback session. Adapted from CHOICES and BALANCE.	Information video condition or information brochure condition.	• AEP risk • TLFB: drinks per dinking day, sexual activity and contraceptive use.	• Significant ↓ AEP risk for intervention (44.9%) compared to either control (video = 63.8%, brochure = 54%) at 6-months. • Significant ↓ ineffective contraception use at 6-months for intervention (44.7%) compared to either control (video = 55.8%, brochure = 50.7%). • All three groups reduced drinks per drinking day with no significant differences between groups.

Study	Intervention	Control	Key outcomes	Key Findings
Ingersoll et al. (2018)	CARRII: 6 web-based weekly sessions adapted from CHOICES.	Same educational content as CARRII but, static and untailored.	• AEP risk • TLFB via online diary for risky drinking and unprotected sex episodes.	• Significant ↓ AEP risk at 6-months for intervention group (36.7%), but not for control group (16.3%). • Significant ↓ ineffective contraception (39.39% at 6-months; $p<0.001$) in intervention group. • No significant changes in intervention (18.18%; $p=0.09$) or control (19.36%; $p = 0.09$) at 6-months for risky drinking.
Manwell et al. (2000)	Project TrEAT: two 15-min physician visits 1 month apart, supportive phone call from a nurse 2 weeks after each visit and workbook with personalized feedback.	Booklet on general health issues.	• TLFB: Alcohol use • Health care utilization: Hospital days, ED visits • Health status: smoking, depression, accidents	• Significant ↓ in 7-day alcohol for intervention ($M = 7.48$ drinks) vs. control ($M = 9.94$; $p = 0.0039$) • Significant ↓ no. of binge episodes past 30 days in intervention ($M = 2.95$) vs control ($M = 4.51$; $p = 0.0021$). • No significant difference in health care utilization or health status.
Montag et al. (2015b)	Assessment + Adapted e-CHECKUP TO GO: single web-based session approx. 20 mins included individualized feedback.	Assessment + treatment as usual	• AEP risk • Drinks per occasion and week • Binge episodes	• All outcomes demonstrated a significant beneficial time effect ($p<.001$), but no intervention effect.
Project CHOICES Research Group. (2003)	CHOICES: 4 face-to-face MI sessions + 1 contraceptive counselling session.	No control	• AEP risk • Alcohol use: AUDIT • Contraceptive use	• 68.5% met at least 1 criteria for change • 12.6% ↓ drinking only • 23.1% ↓ risk of pregnancy only • 32.9% ↓ both drinking and pregnancy risk
Rendall-Mikosi et. al. (2012)	Modified CHOICES: 5 MI face-to-face sessions with contraception integrated in rather than provided as a stand-	Information pamphlet on FAS prevention and a women's health handbook	• AEP risk • Alcohol use: AUDIT • Contraceptive use	• Significant ↓ AEP risk in intervention (50.82%) vs. control (28.12%). • Significant ↓ ineffective contraception use in intervention (42.62%) vs. control (25%).

Study	Intervention	Control	Key outcomes	Key Findings
	alone session. Provided over a 2-month period			• Both groups reduced risky drinking with no significant difference between groups.
Sobell et al. (2017)	Project Healthy CHOICES: Mail-based version of CHOICES in both English and Spanish languages.	Information only – CDC brochures on FAS	• AEP risk • TLFB alcohol use • Contraceptive use	• No differences between intervention and control. • College students significantly less likely than non-students to be at risk of an AEP (OR= 2.09). • Students reduced AEP risk due to effective contraception (p = 0.040).
Tenkku et al. (2011)	Self-guided change intervention: web-based self-guided change intervention with 4 modules designed using individualized motivational messaging.	Mail-based version of the intervention.	• AEP risk • Alcohol use • Contraceptive use	• No difference in effectiveness between mode of delivery. • Both groups reduced AEP risk (mail = 70.6% vs web= 56.7%), quit drinking (mail = 22% vs web=23.1%) and reduced ineffective contraception (mail = 50.8% vs web = 41.2%).
Velasquez et al. (2017)	CHOICES-PLUS: two 40-minutes personalized MI-based face-to-face sessions and contraceptive advice	Brief advice and referral to community services.	• AEP risk • TEP risk • TLFB: Alcohol and contraceptive use • Smoking: self-report 7-day prevalence and saliva test	• Significant ↓ AEP (IRR = 0.620) and TEP risk (IRR = 0.597) in intervention vs. control. • Significant ↓ risk of alcohol use (IRR= 0.784) ineffective contraception (IRR = 0.717) in intervention compared to control. • Reduced risk of TEP reached primarily through use of effective contraception.
Walker et al. (2005)	Educational intervention: assessment + educational brochure about FAS	No control	• Knowledge about risks of FASD	• Significant ↑ knowledge pre-post intervention (p<0.0001).
Wilton et al. (2013)	Adapted Healthy Mom's and CHOICES: 2 MI and cognitive therapy-based sessions delivered via telephone.	2 MI and cognitive therapy-based sessions delivered via in-person.	• AEP risk • TLFB: Alcohol and contraceptive use	• Significant ↓ risk of AEP (100% to 29%), alcohol use (100% to 84%) for both groups. • Significant ↑ effective contraception (0 – 64%), for both groups. • Telephone-based just as effective as face-to-face.

Note. AEP=Alcohol-exposed pregnancy; BALANCE, Birth Control and Alcohol Awareness: Negotiating Choices Effectively; CARRII, Contraception and Alcohol Risk Reduction Internet Intervention; CHOICES, **C**hanging **H**igh-risk Alc**o**hol use and **I**ncreasing **C**ontraception **E**ffectiveness Study; e-CHUG, Electronic Check-Up to Go; eff, effective; FAS=Fetal alcohol syndrome; FASD=Fetal Alcohol Spectrum Disorder; M = mean; IRR = incidence rate ratio; OR=odds ratio; TLFB = timeline follow back; MI = motivational interviewing; CDC = Centres for Disease Control and Prevention; TEP = tobacco exposed pregnancy;

[a] Alcohol use assessed over the past 90 days by asking about 'most drinks,' 'average drinks,' 'average per week,' and how often had '3 or more drinks' and contraceptive use assessed over the past 90 days by asking what type of contraception was used and how often.

[b]depending on drop-out assumptions. Note 100% at risk for an AEP at baseline.

Table 3. Quality of study reporting

Design	Study	Reporting										Ext. validity			Internal validity													P
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
RCT	Ceperich et al. (2011)																											
	Delraheim-Howlettet al. (2011)																											
	Floyd et al. (2007)																											
	Ingersoll et al. (2005)																											
	Ingersoll et al. (2013)																											
	Ingersoll et al. (2018)																											
	Manwell et al. (2000)																											
	Montag et al. (2015)																											
	Rendall-Mkosi et al. (2012)																											
	Sobell et al. (2017)																											
	Tenkku et al. (2011)																											
	Velasquez et al. (2017)																											
	Wilton et al. (2013)																											
BAA	Farell-Carnahan et al. (2013)																											
	Project CHOICES Research Group 2003																											
	Hanson et al. (2017)																											
	Walker et al. (2005)																											
	Hutton et al. (2014)																											
Descriptive longitudinal	Hanson et al. (2013)																											

Note. RCT = Randomised control trial; BAA = Before-and-after; P=Power
Blue = present; Yellow = absent
Questions: 1. Hypothesis/aim/objective 2. Main outcomes; 3. Participant characteristics; 4. Intervention description; 5. Distribution of principal confounders; 6. Main findings; 7. Estimates of random variability; 8. Adverse events; 9. Characteristics of participants lost to follow-up; 10. Actual probability; 11. Invited participants representative of population recruited from; 12. Consented participants representative of population recruited from; 13. Staff, places and facilities representative of participants' usual treatment; 14. Blinding of participants; 15. Blinding of those measuring the main outcomes; 16. Data dredging; 17. Adjustment for different time of follow-up; 18. Appropriate statistical tests used; 19. Compliance with intervention reliable; 20. Valid and reliable outcome measures; 21. Participants recruited from same population; 22. Participants recruited over same time period; 23. Randomization; 24. Concealment of allocation; 25. Adequate adjustment for confounding; 26. Losses of participants taken into account