



THE AUSTRALIAN AND NEW ZEALAND STILLBIRTH ALLIANCE RESEARCH CONSORTIUM

Investigating the causes of stillbirth; a prospective cohort study examining use and effectiveness of a comprehensive investigation protocol

Short title: Investigating the causes of stillbirth

Study Protocol

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AIMS

Stillbirth is devastating to parents, their families and those who care for them. There has been no reduction in stillbirth rates for over two decades. Accurate cause of death data is the cornerstone of effective prevention and essential for parents facing this tragedy to understand *what went wrong*. However, the majority of stillbirths in Australia are not adequately investigated resulting in erroneous data on causation and a high proportion are ‘unexplained’.

This study addresses the call for better data on the causes of stillbirths from the NHMRC Maternity Services review and *The Lancet Stillbirth Series* and constitutes the major research agenda of the Australian and New Zealand Stillbirth Alliance (ANZSA). In this study we will identify causes of stillbirths in a large well-investigated cohort and improve the quality of data on stillbirths across Australia through identifying a cost-effective, evidence-based approach to stillbirth investigations.

SPECIFIC AIMS

Primary

1. To promote the use of the PSANZ clinical practice guidelines (CPGs) for the investigation and classification of stillbirth to a group of level two and three hospitals; to record which tests were done and the value placed on the results; and to use the expert clinical knowledge of a multi-disciplinary team to accurately classify the clinical cause of every stillbirth using the PSANZ Perinatal Death Classification (PDC).
2. To determine the sensitivity, specificity, positive and negative predictive values, and likelihood ratios for the PSANZ stillbirth investigation protocol and its individual tests; to compare diagnostic performance of the PSANZ protocol without autopsy compared to the PSANZ protocol with autopsy.
3. To measure the cost-effectiveness of the comprehensive PSANZ stillbirth investigation protocol compared with a selective approach based on presenting scenarios.

Secondary

1. To improve the consistency of classification across Australia and to contribute to the development of an international classification for stillbirths.
2. To establish a prospective internet-based register on test results of stillbirths to enable a continuous evaluation of the diagnostic tools and aetiologic factors.

HYPOTHESES

1. The rate of unexplained antepartum stillbirth in an unselected cohort will be less than 15% with appropriate investigations and classification by a multidisciplinary committee.
2. Compared to PSANZ protocol with placental examination, the addition of autopsy will increase the sensitivity by at least 10%; that is, it will reduce false negatives by at least 10%, where a false negative is an antepartum stillbirth wrongly assigned to the unexplained category.
3. A selective approach to stillbirth investigations will be cost-effective, that is, it will produce similar outcomes using potentially fewer costs compared with a comprehensive approach.

BACKGROUND

The public health problem of stillbirth

Stillbirth is a devastating pregnancy outcome often resulting in profound and long-lasting adverse psychosocial effects for the mother, father and family¹ and also for their health care providers. While improvements in maternity care resulted in a dramatic reduction in stillbirth in high income countries beginning in the 1940's, more recently, the decline has slowed or halted². In Australia, infant mortality rates have continued to decline³ however, there has been virtually no change in the stillbirth rate in over two decades^{4,5} and some regions show an increase⁶. Of the 292,027 births and 3024 perinatal deaths (stillbirths or deaths of liveborn infants before 28 days of life) in 2007, 2177 (72%) were stillbirths; one in every 130 women reaching 20 weeks gestation will have a stillborn baby⁴, over half occurring in late gestation where survival, if born alive, approaches 100%. Indigenous women have almost twice the rate of stillbirth compared with non-Indigenous women. Unexplained stillbirth occurs at a rate of approximately 2 per 1000 births⁷; which is now around ten times more common than Sudden Infant Death Syndrome (SIDS)³. The scale of this problem was the impetus for the investigators on this submission to establish the Australia and New Zealand Stillbirth Alliance (ANZSA) (a regional office of the International Stillbirth Alliance) and for *The Lancet* to publish a series on stillbirth prevention^{1,2,8-11} including a global call to action⁸. A major focus of this series is the need to improve data on causes and contributing factors for stillbirth. In Australia, approaches to investigation and data on causes of stillbirth are inadequate to inform effective stillbirth prevention strategies. A recent editorial in the Australia and New Zealand Journal of Obstetrics and Gynaecology has called for efforts to improve data quality, and more specifically, for greater uniformity in stillbirth investigation and classification¹².

Risk factors and contributing conditions

With earlier reductions in the stillbirth rates largely due to fewer intrapartum deaths, antepartum fetal death now makes up the majority of stillbirths⁸. Our previous NHMRC-funded project and current meta-analysis of high quality studies¹³, indicate three major potentially modifiable risk factors: maternal overweight and obesity, smoking and advanced maternal age (> 35 years); contributing to over half the stillbirths occurring in high income countries. Factors relating to care are reported to contribute to up to 65% of stillbirths and neonatal deaths². In Australia, while data are lacking, state reports^{6,14} and one detailed study¹⁵ show that contributing factors relating to care are not uncommon. These reported factors often relate to: staff communication, adequacy of antenatal care, detection and management of fetal growth restriction and decreased fetal movements. *The Lancet Stillbirth Series* makes a very clear call for high quality audit to identify areas for practice improvement to reduce avoidable stillbirths^{2,8}. While interventions which address risk factors and contributing conditions are likely to reduce stillbirth, efforts in stillbirth prevention must target specific clinico-pathological causes and conditions².

Standards in investigation and classification in Australia

To enhance accuracy and consistency of data on causes and conditions of stillbirth in Australia, we established the PSANZ Perinatal Mortality Group (PSANZ PMG) and subsequently ANZSA. Through these groups, we have developed, refined, and are now actively implementing the PSANZ Clinical Practice Guideline (CPG) on Perinatal Mortality¹⁶ to improve investigation and audit on causes of stillbirth. In this CPG, we recommend the data that should be collected for each stillbirth, a consensus-based stillbirth investigation protocol (with accompanying information for parents and clinicians to assist in decision making about autopsy examination), a classification system and a process for committee review of stillbirths including identification of contributing factors relating to care. Twenty-six investigations are recommended for stillbirths and a further six tests for thrombophilia at six to eight weeks post partum in specific circumstances¹⁶. While acknowledging that investigation according to this approach may not always be possible or appropriate (e.g. family

wishes)¹⁷, it is recommended as the standard to avoid possible missed diagnoses¹⁸. Due to the often complex nature of stillbirth, and lack of understanding of aetiological pathways, identifying a clear cause is often difficult¹⁹.

We developed the PSANZ Perinatal Death Classification (PSANZ PDC)²⁰ (including user guidelines) for use by multidisciplinary committees to aid in the identification of important clinico-pathological conditions causing or contributing to stillbirth. This 11 major category system has a good²¹ to high²² level of agreement and performs well against other contemporary systems²¹. Unfortunately, uptake of the CPG into practice has been less than optimal²³. Variation in the PSANZ-PDC reported across Australia⁴ indicates inconsistencies in approaches to investigation and classification practices. The lack of evidence for the recommended investigations is thought to be a major factor in suboptimal stillbirth investigation. One population-based study in New South Wales (NSW)²⁴, lead by CIF, showed low agreement between hospital and health department committee reviews indicating the need for education of hospital committees.

We have developed, and are currently rolling out, an educational program²⁵ – IMproving Perinatal Review and Outcomes Via Education (IMPROVE) – which specifically addresses these issues. IMPROVE uses a skills training method which is small-group, participants centred, and multi-professional²⁶. The IMPROVE Program has six stations addressing each major section of the PSANZ Guidelines: Communication with families about autopsy; Classification of perinatal deaths; Examination of a baby who dies in the perinatal period; Psychosocial and social aspects of bereavement care; Placental and post-mortem investigation; and Investigation of perinatal deaths (focussing on stillbirth). However, the lack of evidence for stillbirth investigations remains a major limiting factor to improving uptake into practice.

Causes of stillbirth in Australia

The main clinico-pathological conditions contributing to stillbirth in Australia according to the PSANZ-PDC⁴ are: congenital abnormality (26%); spontaneous preterm birth (often associated with chorioamnionitis) (13%) and specific perinatal conditions (12%) (including twin-twin transfusion and cord complications). The low proportion of stillbirths attributed to certain conditions, such as infection compared with other international series (4% versus 12%¹³ and 24%²⁷), indicates the need for improvement in investigation of stillbirths. Placental pathologies are thought to play an important role in stillbirth¹⁹, virtually replacing the previously unexplained group when classifying with a focus on such pathologies²⁸ and with suboptimal placental pathology rates important pathologies may be currently missed. In pregnancy, thrombophilic disorders are associated with an increased risk of pregnancy complications, with some demonstrating an increase in the odds of stillbirth¹⁹, and while some controversy exists²⁹, thrombophilia may be responsible for some apparently unexplained stillbirths as investigation is often not performed.

Unexplained stillbirth

A high proportion of stillbirths remain unexplained. The lack of diagnosis is difficult for parents struggling to understand *what went wrong* and provides little clues for future prevention. With over 35 different systems internationally²¹, and differing stillbirth definitions and approaches to investigation, wide variation in the reported proportion of unexplained stillbirth exists from 10%²⁷,²⁸ to 70%³⁰. In Australia, using a single classification, variation is still evident; 20%⁶ to 42%²⁴. In our study mentioned above, 30% of stillbirths were unexplained. In this study, detailed analysis of 1740 potentially preventable antepartum stillbirths (excluding those attributed to congenital abnormality) showed the majority (68%) were without a clear cause; 55% were unexplained and a further 13% were associated with otherwise unexplained fetal growth restriction. At term, over 60% of stillbirths were unexplained. However, in this large population-based study, suboptimal stillbirth investigation was evident; autopsy was performed in only 50% and one-third did not have placental histopathology. Other potentially important investigations such as the Kleihauer–Betke for fetomaternal haemorrhage and testing for infection were undertaken in less than half. This low level of

investigation is likely to be representative of investigation across Australia reflected by recent reports of autopsy rates below 50%^{6, 7, 24}**The extent to which the apparent low level of investigation is artificially inflating the number of unexplained stillbirths in Australia is unknown.**

Determining the causes of stillbirth

Determining the causes of stillbirth is an essential part of good patient care. An accurate cause of death may assist in the parents' grieving process by providing an explanation for the death and other information on the circumstances surrounding the death which may alleviate feelings of guilt¹⁹. It is also essential for audit and research aimed at reducing these deaths². When parents and health professionals understand the specific cause of stillbirth, they are able to plan strategies for future pregnancy care. Even when a cause of death is not identified, exclusion of some possible causes is valuable as a reassurance to parents and aids the management of subsequent pregnancies¹⁹. Due to the often complex nature of causation of stillbirth following detailed investigation, the clinico-pathological correlation is best accomplished with review by a multidisciplinary team¹⁹. Based on death certificate data completed at the time of stillbirth (i.e. before full investigation and committee review), the Australian Bureau of Statistics reports the cause of stillbirth as undetermined in approximately 60% of cases³¹. However, following comprehensive investigation and review, the proportion of unexplained stillbirths according to PSANZ-PDC may be as low as 15%^{31, 32}. **Based on these findings it is clear that the cause of stillbirth recorded on perinatal death certificates prior to thorough investigation and review are misleading** and therefore may jeopardise the quality of research and audit activities and subsequent public health policy to reduce stillbirth using these data¹⁶.

Stillbirth investigation protocols – current evidence

A systematic review of stillbirth investigation protocols, and their components³³ identified five formal protocols currently in use, including the PSANZ protocol. While components varied, placental pathology, autopsy, comprehensive maternal history and macroscopic examination of the baby were common to all. However, no studies of sufficient quality were found addressing the performance of protocols and the only tests assessed were autopsy and placental pathology. Five retrospective studies³⁴⁻³⁸ on autopsy showed benefit as follows: confirmed clinical findings in 29% to 89% of cases; changed the diagnosis in 10% to 38%; and provided additional information in 4% to 24%. However, the cause of death remained unexplained in up to 40% of stillbirths. In two prospective studies^{39, 40}, placental pathology confirmed clinical or autopsy findings or both in up to 75% of cases and were diagnostic in 23% to 46%. In these studies, stillbirth remained unexplained in a lower proportion (12%). The authors of this review concluded that **“no formal scientific judgement could be made on which is the most appropriate protocol for stillbirth investigations or which components should be considered for the most relevant and efficient investigative protocol”**³³. Methodological concerns of this review notwithstanding, studies report that comprehensive protocols provide useful information in approximately 30-50% of stillbirths¹⁹. However, the substantial proportion of stillbirths remaining unexplained in these studies (36% to 60%) may reflect less than optimal approaches. A large series from a prospective population based study¹⁷ from a regional referral program in the US reported that a non-selective approach improved the yield of helpful information in 50% of stillbirths. Individual components of the protocol yielded critical information not identified elsewhere whereby exclusion of any single component would result in missed diagnoses from 2% (family history) to 15% (autopsy and placental pathology) of cases. However, the focus of this protocol was on fetal abnormalities and the extent to which maternal investigation was undertaken is unclear. Incerpi et al⁴¹, in a retrospective institution-based study of over 700 stillbirths, showed a high yield from autopsy and placental pathology; however yield for other investigations such as maternal screening for congenital infection and Kleihauer-Betke for fetomaternal haemorrhage was low. This low yield is in conflict with other reports^{42, 43}. The overall autopsy rate in this series was 60%, and the proportion of unexplained stillbirth

remained high (36%). A well conducted study in Stockholm County showed a comprehensive test protocol reduces the number of unexplained cases to a minimum (9%)²⁷.

Costs of stillbirth investigations

There is very limited information available to enable consideration of the cost benefit of stillbirth investigation protocols, or their individual components. Michalski et al.⁴⁴ reported a cost consequence analysis using data from the US referral program described above^{17, 18} showed the real cost of a comprehensive stillbirth protocol was \$1450 per assessment or approximately \$12 per cared-for pregnancy. The authors concluded that the protocol was of sufficient economic value for the comprehensive protocol to become a part of routine antenatal care. **Currently, no economic evaluation study has been undertaken anywhere to enable informed consideration of the economic implications of improving stillbirth investigations in an Australian setting.** Using internationally accepted methods, the proposed study is designed to generate detailed information on the economic efficiency of stillbirth investigation protocols. *Selective and sequential testing.* Selective testing based on clinical features and presumed diagnosis has been proposed as a cost-effective approach^{19, 45}. Lim et al⁴⁵ estimated that a selective approach to investigation of stillbirths would reduce the costs of investigation in 30% of cases without compromising the yield of investigation. However the sample size was small (n=55) and with a low autopsy rate (28%) and a high proportion of unexplained stillbirths (38%), conclusions about the value of this approach can not be drawn.

A recent study in the Netherlands on cytogenetic testing showed that a selective approach based on presenting scenario may miss important causes of stillbirth⁴⁶. Sequential testing, whereby certain tests are undertaken on the basis of results of others has also been proposed as an effective alternative to comprehensive testing¹⁹, however this too has not been tested. **There is currently no available data on the value of either a selective or non-selective or sequential testing protocol for investigation of stillbirths in an Australian setting.**

Autopsy

The process of counselling and consent for autopsy of a stillborn baby is difficult for both clinicians and parents. Parents face an intrusive process that requires understanding detailed consent procedures in a state of grief, making clinicians reluctant to place further burden on the parents⁴⁷. Parents may regret decisions related to autopsy and this may be due to inadequate information provided^{48, 49}. In a pilot study of focus groups of parents who had a recent stillbirth, we confirmed the need for clear information on the value of autopsy to aid decision-making⁵⁰. The autopsy is rated to be useful in establishing a cause of death and in counselling following a stillbirth although many studies do not provide sufficient information to gauge this critically⁵¹. Autopsy examination of an infant is very different to that performed on an adult⁴⁷, and ideally should be performed by a perinatal pathologist.

Pathologists with perinatal training find a higher incidence of causes of death in infants⁵², and provide a much higher proportion of adequate reports^{30, 53, 54}. Cartlidge et al demonstrated an association with higher quality autopsy and the number of perinatal and infant deaths where the main cause of death was identified⁵². Understandably, the ethics of approaching parents for consent where a quality autopsy service is not available has been questioned⁵⁵. Recent studies point to a fall in perinatal, including stillbirth, autopsy rates^{56, 57}. The major limiting factor appears to be parental consent⁵⁸ influenced by cultural and religious beliefs. However, clinician ambivalence about the value of this investigation plays an important role in the current low autopsy rates⁴⁷. The interpretation and reporting of placental pathology can also be variable and is performed better by perinatal pathologists⁴⁷.

While autopsy remains the ‘gold standard’⁵⁹ several protocols are available⁴⁷ and the extent to which each autopsy is performed and the quality and complexity of ancillary testing can account for the integrity and therefore value of the investigation. With the need for high quality and costly pathology services, the stillborn infant often must be transferred to a centre with appropriate facilities, thus increasing costs and anxiety to parents faced with this tragedy. The high emotional burden to parents and resource implications necessitates a better understanding of the value of the autopsy examination.

In summary

1. Data on the causes of stillbirth in Australia are inadequate as a result of suboptimal approaches to investigation. Without an accurate cause of death, appropriate counselling of grieving parents and development of effective prevention strategies is not possible.
2. The PSANZ guideline recommends a comprehensive approach to investigation; however uptake is poor, which is understandable with the current lack of high quality evidence.
3. Autopsy is considered the “gold standard” test for stillbirth. However the intrusive nature of this procedure for parents, access to appropriate expertise and ambivalence about its value has resulted in low autopsy rates for stillbirth.
4. There are no studies in Australia which have adequately examined the causes of stillbirth and none have reported the diagnostic contribution of autopsy in the context of a comprehensive stillbirth investigation protocol or individual components of such a protocol.
5. This study, from an experienced team of researchers, will address these research gaps through detailed examination of a large, well-investigated prospective cohort.
6. Robust data on the diagnostic performance and cost-effectiveness of the recommended comprehensive stillbirth investigation protocol will be used to revise the current PSANZ stillbirth investigation protocol and, combined with our educational program for clinicians, has the potential to improve the quality of data on stillbirths across Australia and reduce stillbirth rates through focussed prevention strategies.

RESEARCH PLAN

Design and study sites

A multi-centre prospective cohort study involving all Level 3 and Level 2 hospitals across Australia where lead clinicians in stillbirth investigation and audit (doctors, midwives and perinatal pathologists) have attended the IMPROVE educational program and implemented the PSANZ guidelines prior to commencement of the study will be included.

Study population

Inclusion criteria: Stillbirths of at least 20 weeks gestation or 400 grams at the participating hospitals will be eligible for inclusion. **Exclusion criteria:** Stillbirths resulting from a planned induction of labour for known fetal anomaly or for maternal psychosocial reasons (i.e. termination of pregnancy) will be excluded from the analyses of data pertaining to the yield from investigations as these cases are not subject to the same level of investigation as other stillbirths. However for completeness, these cases will be included in the descriptive analyses describing the causes of stillbirth for the total study population (Aim 1).

Outcome measures

- Causes of stillbirth classified according to PSANZ-PDC, assigned by expert panel
- Contributing factors relating to care, assigned by expert panel
- Proportion of cases with a changed diagnosis following testing
- Sensitivity, specificity, positive and negative predictive values and likelihood ratios for tests and groups of tests using the expert panel cause of death according to the PSANZ-PDC as the reference (gold standard) classification
- Cost per avoided unexplained death
- Value of information obtained from investigations as rated by hospital committees

Procedure

Identification of study population: All stillbirths fulfilling the inclusion criteria over the study period at the participating hospitals will be included and identified as part of routine procedures within each hospital.

Education of hospital staff: Prior to commencement of the study, the educational program will be undertaken at all hospitals who have not yet participated. The program will target midwives, medical staff and pathologists.

Data collection: Following completion of investigations, the *National Perinatal Death Clinical Audit Tool (NPDCAT)* and PSANZ stillbirth investigation checklist will be completed¹⁶ via a purpose built web-based application. This data collection follows the recommendations within the PSANZ Guideline and should be completed by a senior obstetric registrar or midwife involved in the case. For the economic analysis, the investigation checklists will provide resource data for each case. A health economic supplementary form will also be developed to capture other hospital, staff and time resource data. Additional data items required will be incorporated into the data collection as follows:

1. Participating hospital collection. a) Around the time of stillbirth: Initial details are recorded on the *NPDCAT* by a senior attending clinician including: maternal demographics, obstetric and medical history, and initial understanding of the cause of death. In addition, investigations undertaken will be recorded on the PSANZ stillbirth investigation checklist. This checklist also serves as a prompt for recommended tests; **b) Clinical case summary completion:** The *NPDCAT* and PSANZ stillbirth

investigation checklist will be completed by the clinician for review by the hospital committee; **c) Hospital committee review:** *NPDCAT* completed with the inclusion of the PSANZ-PDC, and the value of the information obtained from investigations.

2. Panel review collection: An expert panel will assign the PSANZ-PDC to each case reviewing all tests performed to determine diagnostic value and the presence of potentially contributing factors. The panel will be blinded to the outcome of the hospital committee review. Autopsy reports will be reviewed and the study autopsy quality criteria applied. As a minimum, the panel will be made up of the CIs on this grant including an obstetrician, a neonatologist, a perinatal pathologist and either CIA or CIB to ensure consistency. Panel members will be excluded from review of cases from their respective hospitals and pathologists from review of their autopsy reports. Each stillbirth will be assigned a lead panel member for presentation and finalisation of data collection through Skype conference. It is estimated that 5-7 hours per month of *Skype* time will be required over a two-year period.

Outcome measurement instruments. Diagnostic yield: The expert panel will review the ability of each test to determine the assigned PSANZ-PDC as follows: Yes, No, Inconclusive or Not performed. Groupings of inconclusive tests which provide the PSANZ-PDC will be assigned as a positive test group. **Contributing factors relating to care:** The PSANZ CPG tool will be used. This tool identifies factors relating to professional practice, health care services, and the women or family. The ascertainment of such factors will be undertaken through consensus of the expert panel using best available evidence from high quality guidelines and Cochrane reviews. **Value of information:** Hospital committees will determine how helpful the information gained from the investigations is to their practice. A measurement tool will be developed using the Delphi Procedure including criteria based on previous studies^{17, 52} including whether the test provided information to assist counselling parents, for future pregnancy planning, or audit. Value of autopsy, and other investigations, to parents forms part of an ancillary study being undertaken in partnership with La Trobe University, Melbourne and the Queensland Centre for Mothers and Babies using a willingness to pay approach and semi-structured interviews. **Autopsy quality:** The assessment criteria developed by Rushton et al⁵³ will be used to assess the autopsy quality. The criteria objectively scores six factors identified by the Royal College of Pathologists⁶⁰ as being part of an autopsy resulting in a maximum score total score of 600, with the minimum acceptable score being 250⁶⁰.

Secondary aims:

Improving consistency of classification and contribution to development of an international system: The PSANZ-PDC assigned by the panel will be compared with that applied by the hospital committees as a learning opportunity for hospital committees. This information will be provided for individual hospitals by CIs and AIs attending meetings and through a revision of the PSANZ-PDC Guidelines for use. The panel will also apply a proposed system for mapping current clinical classifications¹¹ for the purpose of enabling valid comparisons across low, middle and high income countries. Several countries are planning to participate in this activity which is coordinated through the International Stillbirth Alliance. Such a system will help to identify and monitor interventions to reduce stillbirth globally particularly in regions with the highest stillbirth rates⁸.

Establishment of a prospective collection for stillbirths: Collaboration across regions and countries is essential to effectively reduce stillbirth, and the need for comprehensive prospective data collection on stillbirth is increasingly acknowledged. Surveillance and research collections are now underway in the USA, through the Centre for Disease Control (CDC) and the NICHD Stillbirth Collaborative Research Network and also in the Netherlands. This submission will provide the opportunity to evaluate the feasibility of a prospective internet-based register on test results of stillbirths to enable a continuous evaluation of the diagnostic tools and aetiologic factors and enable addition of a temporaneous control group to address high priority research questions effectively.

Sample size

Hypothesis 1 concerns the percentage of unexplained antepartum stillbirths; reports of which have varied greatly from 10-70%²¹. We do not know the current percentage of unexplained antepartum stillbirths in Australia or what the percentage would be if PSANZ guidelines were followed. However, based on our previous work we estimate this to be around 30% and implementation of the PSANZ protocol and classification of clinical cause by a multidisciplinary team could result in a decrease to about 25%, or perhaps even to <15%. With a sample size of 604 we will have 90% power to discriminate an unexplained percentage of 15% from 20% with 95% confidence (i.e., $\alpha=0.05$ in a hypothesis testing framework). A sample size of 731 will allow us to discriminate an unexplained percentage of 20% from 25% and 836 will allow us to discriminate 25% from 30%⁶¹ (with 90% power). As discussed, it is extremely unlikely that the unexplained percentage will not be as low as 25%, therefore 836 is an upper limit for the number of antepartum stillbirths required. We expect that 10 to 15% of stillbirths will occur intrapartum. Therefore, a sensible upper limit for sample size is 984 [$836/(1-0.15)$].

Hypothesis 2 relates to the additional benefit of autopsy in reducing the number of stillbirths classified as unexplained. Interest therefore centres on the false-negative rate (or the percentage $a/(a+c)*100$) in Table 1.

Complete testing, excluding autopsy	Complete testing		
		Explained	Unexplained
	Explained	'a	'b
	Unexplained	'c	'd
	'a+c	'b+d	

Table 1. Two by two table showing testing relating to hypothesis 2. [note: b (false-positive rate) will be small]

Given that we are comparing the PSANZ protocol with and without autopsy, it is unlikely that the false-negative rate is more than 20%. If the false-negative rate is as large as 20%, then a sample size of 245 would allow us to estimate it to within +/-5% with 95% confidence⁶². Smaller (and arguably more plausible) false-negative rates could be estimated more precisely. Table 1, given in the paper by Flahault and co-authors (and not reproduced here because of space restrictions), shows that 245 is a suitable sample size for plausible values of the false-negative rate⁶³. To arrive at the sample size for stillbirths in the study who have all tests, the value of 245 has to be adjusted for the prevalence of unexplained stillbirths: $(b+d)/(a+b+c+d)$ in the Table 1 (above)⁶³. For the group of stillbirths, who have had all the tests, an upper limit for prevalence is 25% (as above)⁶³, which gives $N_{\text{unexplained}} = 245 \times (.25/.75) = 82$. This gives a sample size for stillbirths in the study who have all diagnostic tests of $245 + 82 = 327$. If the prevalence of unexplained stillbirth is lower than 25% (as is likely), then the study will be more precise than we have estimated. **Then**, the number of stillbirths who have all tests has to be inflated to accommodate the group that do not have an autopsy. In our population-based study of stillbirths (2000-2003) in three states (QLD, WA, VIC), 46% of stillbirths had an autopsy. We therefore used 46% as a lower bound for sample size calculations. Using this calculation we obtain a sample size of 711 ($327/0.46$). Higher autopsy percentages, which are possible, given the inclusion criteria for hospitals in this study (workers attended the IMPROVE education program, PSANZ guidelines implemented), would result in more statistical power and more precise results. That is, our assumptions were conservative. **Finally**, we expect that 15% of stillbirths will occur in the intrapartum period. Therefore, a sensible sample size is $711/(1-0.15)=837$. This is slightly less than for the first hypothesis ($n=984$).

Data management and statistical methods: Data from participating institutions will be entered by local study coordinators into a web-based application developed and maintained by the main coordinating centre at the Mater Medical Research Institute (MMRI).

Aim 1. Clinico-Pathological cause of stillbirth. The primary analysis will use descriptive statistics of percentages with 95% confidence intervals (CI) to present causes of death according to the PSANZ PDC. Secondary analyses by gestation at birth (≥ 28 weeks and < 28 weeks), timing of death (antepartum and intrapartum) and Indigenous status.

Aim 2. Diagnostic test performance. Sensitivity, specificity, positive and negative predictive values and likelihood ratios⁶⁴⁻⁶⁶ will be calculated comparing the full stillbirth protocol with autopsy examination with the protocol minus the autopsy. These parameters will also be calculated for each test and groups of tests using the classification of death by the expert panel as the reference standard. Subgroups analysis will be undertaken by autopsy quality and presenting scenarios as follows: 1. Intrapartum stillbirth after 34 weeks gestation; 2. Preterm rupture of membranes; 3. Catastrophic event (i.e. major acute placental abruption, uterine rupture, cord prolapse); 4. Fetal growth restriction detected antenatally or at birth; and 5. No probable cause at birth. **Verification bias:** For this study, the reference standard requires having the complete suite of non-selective PSANZ stillbirth investigations. Therefore, to assess the additional benefit of autopsy, we will only consider those stillbirths, for whom the complete suite of investigations was done, as specified in the non-selective PSANZ stillbirth investigation protocol. This might cause a bias in that those stillbirths, for whom the diagnosis/cause is obvious, might not have the full suite of tests. We will be able to assess this because we will have data on all stillbirths and if necessary will adjust for it in the analysis using methods developed to adjust for verification bias⁶⁷⁻⁶⁹. To supplement this analysis we will calculate the value of the investigations and groups of investigations by presenting scenarios using the purpose built tool previously described.

Aim 3. Cost-effectiveness. A cost-effectiveness analysis will be undertaken to assess the resource costs and benefits for the non-selective approach to stillbirth investigations compared with a group which receive selective investigations for presenting scenarios. Data for the selective care group will be based on a subgroup of participants not receiving the PSANZ recommended testing protocols. The economic study will take a health provider perspective (participating maternity hospitals) and involve the assessment of 1) resource use, by identifying, quantifying and valuing resources involved for each participants in the protocols using standard methods⁷⁰; and 2) benefits, in terms of the number of avoided unexplained stillbirths. This outcome forms the cornerstone of flow-on benefits, namely minimising misclassification for monitoring systems, providing more information to distressed families and facilitating future reproductive decisions and antenatal care. Protocol resources will be recorded prospectively by the researchers and broadly categorised, such as clinical examinations, autopsies, pathology, diagnostic assessment and follow-up counselling. Costs will include each investigation including staff time, materials used and an estimated institutional overhead cost component. The costs of additional non-recommended testing will also be highlighted. We will seek assistance from hospital clinical costing departments to provide a monetary value for investigation resources (unit costs) and Dr Gordon has used this method in her previous work. For the analysis, we will combine cost and outcome data into incremental cost per benefit ratios. This represents the additional cost of the comprehensive stillbirth protocol over and above the selective protocol, for an additional avoided unexplained stillbirth. We will use Australian epidemiological data to extrapolate the findings Australia-wide and analyse the scenarios of interest using modelling software TreeAge Pro (Healthcare Module) 2011. Simple and probabilistic sensitivity analysis will be undertaken to address data uncertainty and potentially strengthen the generalisability of the results. Specifically, Monte Carlo simulations will produce cost-effectiveness acceptability curves and probabilistic statements on cost-effectiveness. Additional multiple regression analyses on total costs will be undertaken to explore the main cost

determinants in further detail. Attention will be given to the statistical analysis of observational data comparisons across the two groups.

FEASIBILITY AND TIMELINE

The successful collaborative work undertaken by this team, through the PSANZ PMG and ANZSA, ensures the success of this study. In principle agreement has been received from 17 hospitals with a total of 70,000 births annually. Based on data from our previous study, the estimated stillbirth rate across these centres is 9/1000 providing 567 stillbirths annually. Assuming a compliance rate for data collection of 90%, and exclusion of 10% as per study criteria, we estimate 500 stillbirths per year will be included and the sample of 984 achieved within a two year period.

OUTCOMES AND SIGNIFICANCE

The core aim of stillbirth investigation is to provide quality care to distressed families, to provide critical information to improve service delivery, knowledge and research and ultimately, to prevent future stillbirths. A comprehensive approach to the investigation of stillbirths is currently recommended by PSANZ. However, implementation is suboptimal, driven by a lack of evidence on the value of this approach. The high proportion of unexplained stillbirths is a major barrier to further improvement in the stillbirth rate. Accurate data on the causes of stillbirth are needed and we require better evidence on the efficacy and value of stillbirth investigations along with the resource implications for health providers, which this project will deliver. Only when stillbirth causes are accurately investigated and defined will it be possible to institute and evaluate specific preventive strategies to reduce the frequency of these deaths.

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Version control

Date	Version	Change	By whom	Comment
April 4 2011	1.01		Vicki Flenady	Protocol submitted to NHMRC
Feb 6 2012	1.02	Addition of collaborators under Investigator team	Vicki Flenady	
April 27 2012	1.03	Addition of collaborators under Investigator team and identification of steering committee	Vicki Flenady	
May 21 2012	1.04	Addition of collaborators under Investigator team	Vicki Flenady	
May 25 2012	1.05	Addition of collaborators under Investigator team	Vicki Flenady	
June 19	1.06	Addition of collaborators under investigator team	Paul Gardiner	
July 19	1.07	Addition of collaborators under investigator team	Vicki Flenady	
August 8	1.08	Addition of collaborators under investigator team	Vicki Flenady	
December	1.09	Updating references and exclusion criteria	Paul Gardiner	Updated to reflect version submitted to HRECs
March 16 2013	1.10	Addition of collaborators under investigator team	Paul Gardiner	All site PIs are now listed as investigators
September 19	2.1	Updating Feasibility and timeline & Outcomes and significance	Hanna Reinebrant	Updated to reflect HREC approved protocol