

# NIHR HTA Programme

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## SABRE Protocol

**FULL TITLE: Hypertonic Saline in Acute Bronchiolitis: Randomised Controlled Trial and Economic Evaluation**

**SHORT TITLE: SABRE (hypertonic Saline in Acute Bronchiolitis Rct and Economic evaluation)**

**REC REF: 11/YH/0101**

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### **LAY SUMMARY (max 300 words):**

This is a multicentre randomised controlled trial which aims to determine whether the addition of 3% hypertonic saline to usual care results in significant [25%] reduction in the duration of hospitalisation of infants with acute bronchiolitis.

Infants will be randomised to receive nebulised 3% hypertonic saline in addition to supportive care (n=150) or standard supportive care (n=150).

The primary outcome will be time to 'fit for discharge' using criteria based on those proposed in the UK Scottish Intercollegiate Guidelines Network [SIGN] Bronchiolitis in Children guideline. Secondary outcomes will include the economic impact of such an intervention on both the National Health Service (NHS) and parents, as well as quality of life and other health related outcomes 28 days after entry to the study using a questionnaire and research nurse telephone contact.

Sheffield Children's   
NHS Foundation Trust



## GENERAL INFORMATION

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## **GLOSSARY**

### **List of abbreviations used**

AE	Adverse Event
CRF	Clinical Research Facility
CTRU	Clinical Trials Research Unit
CUA	Cost-Utility Analysis
DMEC	Data Monitoring and Ethics Committee
ITQoL	Infant Toddler Quality of Life questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HDU	High Dependency Unit
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ICU	Intensive Care Unit
LOS	Length Of Stay
MAE	Major Adverse Event
NHS	National Health Service
RSV	Respiratory Syncytial Virus
SD	Standard Deviation
TMG	Trial Management Group
TSC	Trial Steering Committee
QALYs	Quality Adjusted Life Years

## 1.0 BACKGROUND

This is a protocol for a randomised controlled trial. Its primary hypothesis is that the addition of 3% hypertonic saline to usual care results in significant (25%) reduction in the time to when infants admitted with acute bronchiolitis are 'fit for discharge'. Secondary hypotheses are that the addition of nebulised 3% hypertonic saline to usual care is associated with:

- improved quality of life outcomes for carers
- shorter length of stay
- improved quality of life for the infants
- reduced health care utilization in the month after discharge
- cost effectiveness for the NHS
- the effect is independent of the underlying virus

Acute bronchiolitis is the commonest cause for hospitalisation in infancy and childhood with 1–3% of all infants being admitted to hospital during their first winter [1-8]. Common respiratory viruses cause obstruction of the airways, infecting the lungs, leading to severe difficulties in breathing [1-12]. The majority of babies admitted with this condition are under six months of age and the associated stress for parents is considerable.

The only intervention that has had a major impact on the survival of infants is oxygen therapy which has reduced mortality rates from around 20% to less than 1% [27]. Otherwise, currently treatment consists of providing good supportive care until the infant recovers [4,22,23]. There were some 30,000 admissions for acute bronchiolitis in 2009/10 in England (64) and such epidemics place enormous strains on paediatric services and Intensive Care Units (ICU) [4,8,14] which sometimes have to close due to the numbers of infants with acute bronchiolitis[14-16].

A number of relatively small studies published over the past eight years[43-46] have suggested that nebulised hypertonic saline may influence the course of the illness resulting in a reduction in the duration of hospitalisation for infants admitted to hospital with 'acute bronchiolitis'. A subsequent Cochrane review[47] undertook a systematic review of the literature focusing on these four trials which involved a total of 254 infants with 'acute viral bronchiolitis' of whom 189 were inpatients and 65 patients were treated in the emergency department. They concluded that "current evidence suggests nebulised 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis." The conclusions do not go beyond suggesting this intervention may have an impact because of the methodological limitations of the included studies and the potential for publication bias. They noted that the conclusions are further limited by the small number of subjects included in each study and consequent low power; the different settings since inpatients and outpatients were included and the failure to show a difference in some outcomes such as the failure to reduce hospitalization in the outpatient groups. Despite these limitations, some hospitals in the United Kingdom (UK) have already adopted this approach to treatment.

Its mode of action is believed to be through alteration in mucus rheology as a result of improved hydration and the breaking of ionic bonds within the mucus leading to improvements in mucociliary and clearance of secretions[48,49]. The observation that hypertonic saline can increase ciliary beat frequency could further enhance clearance[48]. It is also suggested that this intervention reduces mucosal wall oedema through osmotic effects. There is good evidence that bronchoconstriction does not contribute significantly to the airways obstruction in infants with acute bronchiolitis which explains why bronchodilators do not provide any benefit [33-36]. Instead the obstruction appears to be in part due to oedema within the airway wall and, probably more importantly, accumulation of inflammatory exudates in the airways. Significant impairment of mucociliary clearance due to shedding of ciliated cells compounds the problem and contributes to accumulation of secretions in the small airways. Hence an intervention leading to improvement in clearance of these secretions and reduced airways wall oedema may well be of benefit in infants with acute bronchiolitis and this is believed to be the mechanism through which the hypertonic saline is believed to act.

In contrast to these positive studies a recent Canadian study based in an Emergency Department found no benefit when nebulised 3% hypertonic saline was added to 'usual care'[50] while a second study from Turkey, again involving non-hospitalised children[51], found that 3% hypertonic saline offered no advantage over nebulised normal saline in addition to 'usual' care. In both cases the intervention was in addition to the use of bronchodilators. Understanding the differences in terminology used in North America and the UK is key to understanding why these studies might be predicted to have a negative outcome and are not directly relevant to UK practice.

In North America and a number of other countries the term 'acute bronchiolitis' is generally used to describe an infant or young child with an apparent viral infection who is experiencing their first episode of wheeze[2,5,30]. In the UK, Australia and some Northern European countries the key feature of infants with acute bronchiolitis is the presence of widespread crepitations on auscultations rather than wheeze which may or may not be present[2,4,30]. In general those with wheezing illnesses labeled as acute bronchiolitis are somewhat older [mean 9-15 months][52-54] than infants admitted in the UK with acute bronchiolitis in whom the peak age for admissions is around 4 months of age[52,55-58].

The clinical phenotype of subjects included in a study has been shown to be important not just in the acute illness but in terms of subsequent morbidity with those having the 'North American phenotype' being much more likely to subsequently shown to have asthma than those with 'acute bronchiolitis' as defined in the UK which is not associated with development of atopic asthma[52,59].

These subtle but very important differences in inclusion criteria are likely to explain some previous apparently contradictory results in this area. For example some[53,54], but not all, studies assessing the possible efficacy of nebulised adrenaline in treating young children with acute bronchiolitis in North America have had a positive outcome but when trialed in the UK and Australia it was found to be ineffective with potential side effects[55,56]. In contrast to experience with bronchodilators it is possible that hypertonic saline will be more effective in acute bronchiolitis as understood in the UK in that its putative modes of action would address the dominant mechanisms of airways obstruction in these patients while it would be expected to have little or no effect in those with wheeze in whom there was significant bronchoconstriction. The studies from Canada and Turkey included children in an outpatient

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setting with an inclusion criteria of wheeze. Predictably their mean age was significantly higher than the population admitted to UK units with 'acute bronchiolitis' and represent a different phenotype often referred to as wheezy bronchitis or viral associated wheezing in the UK.

The observation that the greatest benefit from the use of nebulised hypertonic saline appears to be in hospitalized infants with a similar age distribution [mean 2 – 4months] [33-35] to that seen in UK centres [44-46] would support the potential of this approach in a well defined UK population of infants admitted with acute bronchiolitis. Moreover the mean duration of stay in the control group in all three studies was 3.5 days again consistent with UK practice. The reduction in duration of inpatient stay in the three studies was 25-27%[33-35].

An inexpensive intervention that reduces hospitalization by 25% would be of considerable value to the NHS and is likely to have a significant impact on the levels of stress experienced by young parents with an acutely ill infant. Some paediatric units in the UK have already adopted this approach on the basis of the Cochrane review. However, it is possible that publication bias and poor study design has resulted in a false positive outcome and, if this were the case, there is the potential for an ineffective therapy to creep into practice. Conversely there is a significant risk that uncritical acceptance of the ambulatory studies may lead to discarding an potentially effective therapy through inclusion of a different patient population given the same clinical diagnosis.

In light of the uncertainties surrounding this potential valuable therapy it is essential to undertake an appropriately powered study in a clearly defined UK population to determine whether there is indeed reason for UK paediatric units to adopt this approach or whether it should simply be add it to the list of potential therapies known not to have a significant clinical impact. The importance of undertaking such a study has been recognized both by the Paediatric Respiratory Studies Group and by observers in countries with similar health care systems and diagnostic criteria such as Australia[60].

## 2.0 TRIAL OBJECTIVES AND PURPOSE

The purpose of the trial is to evaluate the clinical and cost-effectiveness of hypertonic saline in the treatment of acute bronchiolitis. The primary objective is an analysis, which will show if the addition of 3% hypertonic saline to usual care results in significant [25%] reduction in the duration of hospitalisation of infants admitted with acute bronchiolitis. The secondary objectives are assessments of the economic impact of such an intervention on both the NHS and parents, as well as quality of life and other health related outcomes assessed 28 days after entry to the study.

## 3.0 TRIAL DESIGN

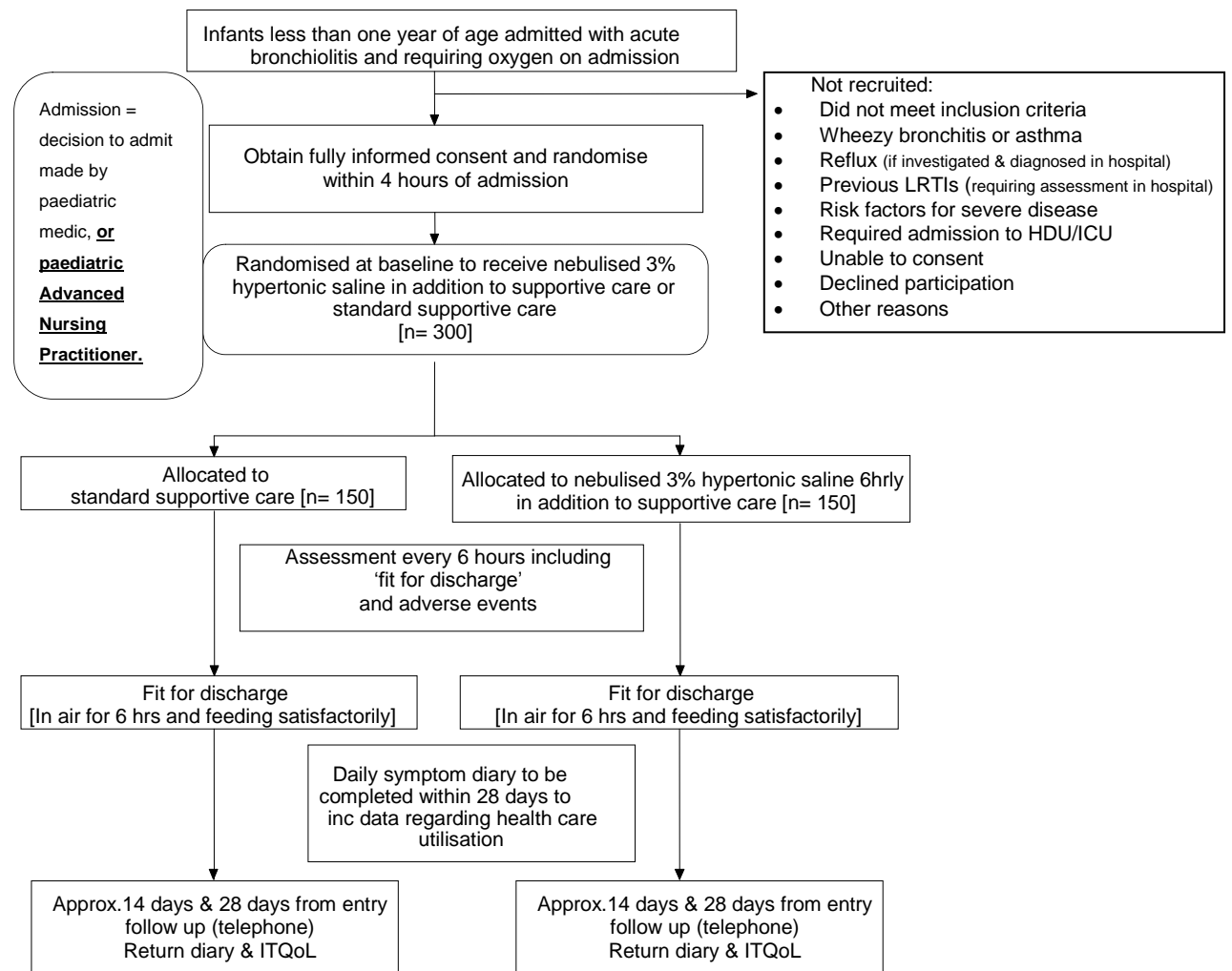
This is a medical devices trial. It is an individually randomised controlled trial comparing the addition of nebulised hypertonic saline to usual supportive care in a cohort of infants admitted with acute bronchiolitis. The expected duration of patient participation and follow-up will be 28 days in total from date of hospital admission/entry to study.

	Before baseline	Baseline	Every six hours	After discharge	28 days after randomisation
Eligibility criteria applied by medics	✓				
Participant information sheet offered by nurses	✓				
Informed consent by medics or delegated nursing staff	✓				
Baseline demographic		✓			
Randomisation		✓			
Apply 'fit for discharge' criteria		✓	✓		
Diary – symptoms and health service utilisation				✓	✓
ITQoL					✓
Nurse telephone call to confirm diary and health service utilisation				✓	✓
Safety assessments			✓		✓
Ongoing monitoring		✓	✓	✓	✓
Retrospective identification of additional adverse events				✓	✓

## CONSORT chart

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## Primary and Secondary Endpoints

### Primary endpoint

The primary outcome will be time to 'fit for discharge', which will be judged to be when the infant is feeding adequately [taking >75% of usual intake] and has been in air with a saturation of at least 92% for 6 hours, to reflect clinical practice.

### Secondary endpoints

- Actual time to discharge
- Readmission within 28 days from randomisation
- health care utilisation, post-discharge and within 28 days from randomisation;
- duration of respiratory symptoms post discharge and within 28 days from randomisation
- Infant and parental quality of life using the Infant Toddler Quality of Life (ITQoL) questionnaire at 28 days following randomisation.

## **Trial Interventions**

3% hypertonic saline is licensed as a medical device in the UK under the brand name MucoClear® and is indicated for the mobilisation of secretions in the lower respiratory tract in patients with persistent mucus accumulation such as those with acute bronchiolitis or cystic fibrosis. It is presented as a 4 ml plastic ampoule for nebulisation and comes in packs of 20 or 60. The product contains no preservatives and has an expiry date of 3 years from manufacture. The product will be administered via the PARI Sprint. The dose to be administered is 4 mls every 6 hours, in accordance with previously published studies. It will be administered by a nurse, with infants inhaling the aerosolised saline. The saline will be discontinued once the 'fit for discharge' criteria has been met – in air for 6 hours with oxygen saturations of at least 92% and feeding satisfactorily.

For the purpose of this trial, MucoClear® 3% will be sourced by and dispensed locally from each site's Pharmacy Department. While this is not a clinical trial of a medicinal product and therefore not subject to The Medicines for Human Use (Clinical Trials) Regulations 2004, the Principal Investigator in conjunction with their local Pharmacy Department will ensure that the principles of Good Clinical Practice (GCP) are applied to ensure robust accountability of the supply and administration of 3% hypertonic saline.

### *Other medications*

**There is no proven drug therapy for the treatment of bronchiolitis. Anti-pyretics (paracetamol and/or Ibuprofen) are recommended for pyrexia and pain management.** Nappy rash cream, Gaviscon, Dioralyte and Lactulose (and related generic medications) are permitted.

Antibiotics are **permissible** for suspected secondary bacterial infections (e.g. due to x-ray changes). Saline can be continued if bronchiolitis remains the primary diagnosis.

Record all concomitant medications. The use of antibiotics, saline nasal drops, and hypertonic saline given after an infant is declared fit for discharge, will be investigated in the analysis as possible confounders.

### *Discontinuation of prescribed drugs*

It is routine clinical practice to discontinue antibiotics previously prescribed by GPs. Antibiotics are not recommended in any 'bronchiolitis' guideline, including the SIGN UK guideline, and published data has suggested their use is associated with a significant level of adverse event with no discernable benefit.

### *Known and potential risks to human subjects*

3% hypertonic saline is by and large a non-invasive treatment. There is the potential for distress associated with applying the facemask and coughing induced by inhaling the saline though both are generally relatively uncommon, minor and transient.

The treatment does not involve radioactive substances.

The trial will start with the first patient's informed consent signed. The last patient's last protocol-defined assessment will mark the end of the trial.

#### 4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

##### Source of subjects

The target population will be infants less than 12 months of age admitted to hospital with a clinical diagnosis of acute bronchiolitis and requiring supplemental oxygen as part of routine supportive care. Subjects will be recruited from the paediatric wards and assessment units of the nine participating centres between October 2011 and March 2013.

##### Inclusion criteria

- Previously healthy infants under 1 year of age
- Admitted to hospital with a clinical diagnosis of acute bronchiolitis, following the UK definition of an infant with an apparent viral respiratory tract infection associated with airways obstruction manifest by hyperinflation, tachypnoea and subcostal recession with widespread crepitations on auscultation [4]. **Admission is defined as the point the medical paediatrician, or paediatric Advanced Nursing Practitioner, makes the decision to admit. (Current perspective is Advanced Nursing Practitioners are equivalent of Specialty Trainee 1 – Specialty Trainee 3 / Senior House Officer.)**
- Requiring supplemental oxygen therapy on admission (either the infant is already in oxygen or oxygen is recommended at the point of admission).
- Consented and randomised within 4 hours of admission by a medical paediatrician

##### Exclusion criteria

- Wheezy bronchitis or asthma – children with an apparent viral respiratory infection and wheeze with no or occasional crepitations
- Reflux (if investigated and diagnosed in hospital)
- Previous lower respiratory tract infections (requiring assessment in hospital)
- Risk factors for severe disease [gestation <32 weeks, immunodeficiency, neurological and cardiac conditions, chronic lung disease]
- Subjects where the carer's English is not fluent and translational services are not available
- Requiring admission to high dependency or intensive care units at the time of recruitment

## **Withdrawal of subjects**

- In the event that a parent/guardian requests withdrawal from the trial, any data collected prior to withdrawal will be retained, as stated in the Participant Information Sheet.
- A patient whose treatment is withdrawn or changed will remain in the trial follow up as per intention to treat principle.
- Patients admitted to the PICU or HDU will be withdrawn from the trial treatment but, unless parents/guardians expressly request withdrawal from the trial, we will continue to follow-up patients for outcome data.

If a patient develops a co-morbidity the end point will remain 'fit for discharge' according to respiratory criteria (i.e. the patient may remain in hospital because of co-morbidity e.g. meningitis).

## **Protocol non-compliances**

**Every effort must be made to avoid protocol non-compliances. Participating centres are asked to note the following:**

- **In the case that the person consenting is called away in an emergency before randomizing, do not then attempt to randomize the patient if this will take place outside 4 hours from admission (decision to admit – see Inclusion Criteria page 10).**
- **Do not randomise patients without written consent.**

## **5.0 SUBJECT RECRUITMENT**

In line with previous experience in undertaking studies in this patient population, recruitment will be undertaken by GCP-trained **Specialty Trainee (ST 1-8) paediatricians and consultants, or staff of equivalent training** (e.g. GCP-trained paediatric nursing staff responsible for acute admissions). They will approach parents/guardians at the point of first contact, as soon as the infant has been identified as eligible for the study. Written information will then be provided to parents/guardians willing to consider their infant taking part in the study. If agreed, written informed consent will be obtained from the parents/guardians by **Specialty Trainee (ST 1-8) paediatricians and consultants, or staff of equivalent training** (see above). It is our experience that recruitment to such studies, in which infants are being admitted every single day, is far less problematic than recruitment to studies involving acutely ill patients with conditions that present less frequently.

Due to the acute nature of the condition it will not be possible to follow a usual timeframe between receiving information and giving written informed consent of at least 24 hours. However, every opportunity will be taken to ensure that parent/guardians fully understand the implications of taking part in our study. They will be invited to ask questions and reflect prior to signing the informed consent document. If interpreters are required primarily for a child's clinical care and it is feasible, these resources will be utilised for the trial. No payment will be offered to participants.

## **Randomisation**

The recruiter will enter the participant's details onto an online system and be asked the following:

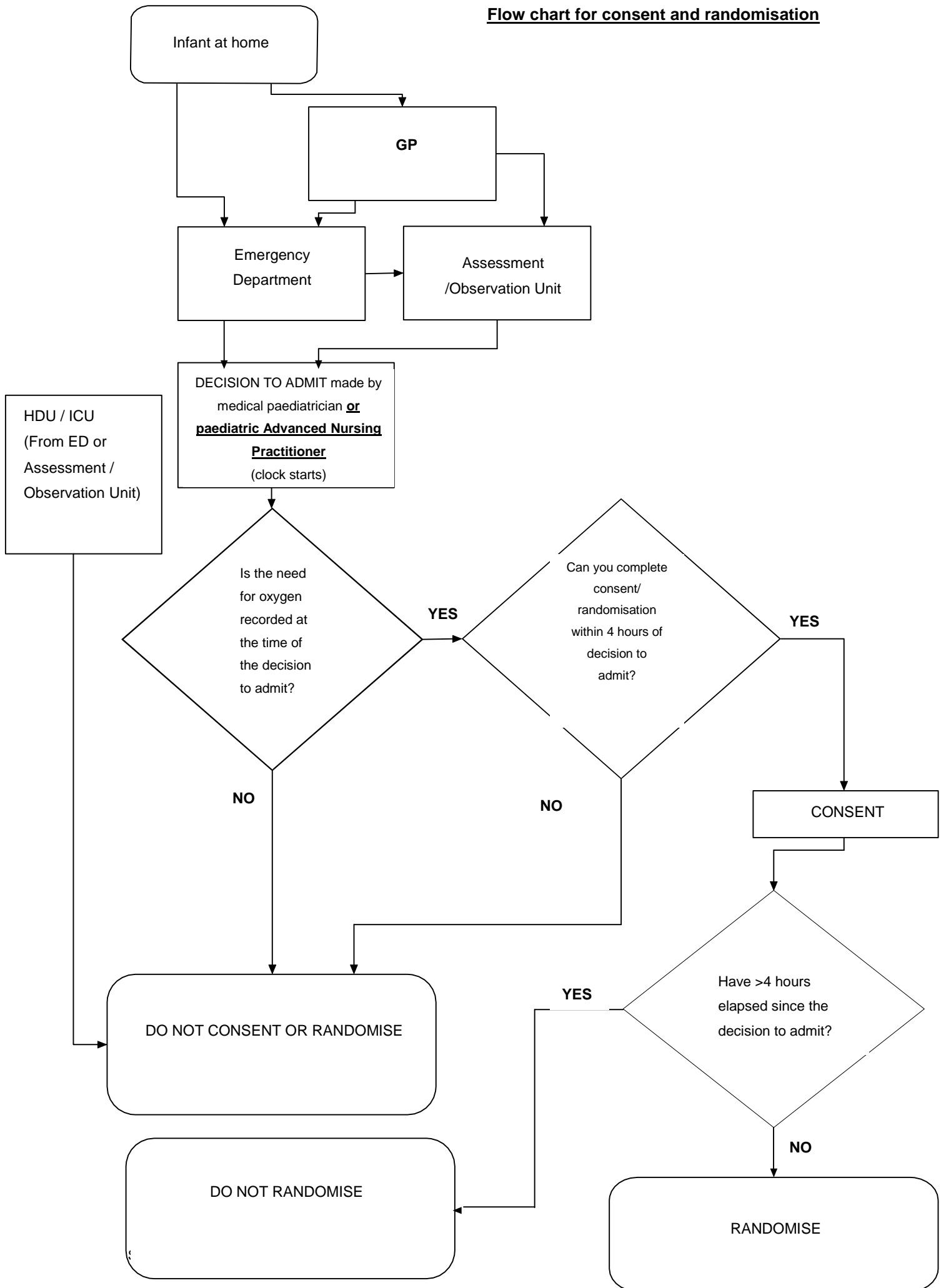
- to confirm written consent has been received
- to confirm the participant is in **oxygen**
- to enter the time a medical paediatrician made the decision to admit (see definition under Inclusion criteria, page 10)

The system will only allow randomisation if the current time is within 4 hours from the time of decision to admit. Please also refer to the flow chart, page 13.

Participants will then be randomly allocated via the online system to receive either: a) hypertonic saline with usual care (n=150), or b) usual care (n=150). Once randomised, participants are irrevocably entered into the trial.

The randomisation schedule will be generated prior to the study by the Clinical Trials Research Unit (CTRU) Randomisation Service. The allocation schedule will be concealed through the use of a centralised web-based randomisation service, which also allows unblinding in the case of emergency. The randomisation sequence is computer-generated and will not be revealed to any person involved in patient recruitment.

**Flow chart for consent and randomisation**



### **Blinding and other measures taken to avoid bias**

The study is unblinded and will compare the addition of the intervention to usual care without placebo. The use of placebo in this setting is problematic in that this would involve an intervention that may have a significant effect on the outcome for subjects in the 'placebo' arm. The extra handling involved in nebulised therapy may have a deleterious effect as has been shown to be associated with the increased handling associated with physiotherapy[40]. Similarly the 'placebo' agent may cause harm as has been suggested in previous studies using nebulised distilled water or may have an unexpected positive impact for an agent such as a normal saline[50].

### **Data collection**

The source of data will be:

- patient notes and hospital computer systems (for 'fit for discharge'; actual time to discharge; and readmission)
- diaries assessing symptoms and health service utilisation. These will be given or posted to parents/guardians at discharge from the hospital and completed during 28 days post-randomisation
- postal questionnaire, the Infant Toddler Quality of Life Questionnaire (ITQoL), completed at 28 days post-randomisation

The ITQoL is a standardised quality of life questionnaire that has been validated for use in infants aged two months to five years [65]. The questionnaire is completed by a parent or guardian. It covers 13 domains, including three relating to parental health related quality of life and it has been used successfully in a respiratory illness sample similar to this study, with a response rate of 79.7%.

Assessment of fitness for discharge will be at baseline, then 6 hourly until "fit for discharge" criteria have been met. Research nurses will record baseline demographic data, co-interventions, and outcome data on the Case Report Form (CRF). Research nurses will also collect basic anonymised details (e.g. age, reason for admission) on all eligible patients to allow completion of a CONSORT flow chart. To assess worsening of condition since discharge and maximise completeness of data, research nurses will telephone parents/guardians approximately 14 days post-randomisation. Non-responders after the 28 days will be contacted by the research nurse and sent a further ITQoL questionnaire if appropriate. The parents/guardians and infant's involvement in the trial will then end.

## **6.0 DATA HANDLING AND RECORD KEEPING**

Data input will be the responsibility of research nurses. Data quality is the responsibility of the Sheffield CTRU Trial Manager and the CTRU Data Management Team. The detailed data management and data quality issues will be set out in a data management and monitoring protocol.

Data will be collected and retained in accordance with the Data Protection Act 1998. Anonymised trial data will be entered into a validated database system designed to a specification agreed between Sheffield CTRU and the Chief Investigator. The system will be accessible remotely via a web browser, with the data stored securely on a central server. Access will be controlled by the use of assigned logins and encrypted passwords. The system will have a full electronic audit trail and will be regularly backed up. Quality control procedures will be applied to validate the trial data. Error reports will be generated where data clarification is required. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Chief Investigator. Trial documents (paper and electronic) will be retained in a secure location during and after the trial has finished.

All source documents will be retained for a period of at least 5 years following the end of the trial. Where trial related information is documented in the medical records those records will be retained for at least 5 years after the last patient last visit. Each site is responsible for ensuring records are archived and the information supplied to the Chief Investigator.

## **7.0 ACCESS TO SOURCE DATA**

The sponsor will permit monitoring and audits by the relevant authorities, including the Research Ethics Committee. The investigator will also allow monitoring and audits by these bodies and the sponsor, and they will provide direct access to source data and documents.

## **8.0 STATISTICAL ANALYSIS**

### **General considerations**

A full statistical analysis plan has been developed. At the request of the DMEC, one interim analysis will be undertaken in July 2012. The DMEC may recommend that recruitment to the study is terminated if the primary outcome (time to fitness for discharge) is significantly shorter in the saline group at the  $\alpha=1\%$  level of statistical significance. An  $\alpha=4.5\%$  level of significance will be used for the final analysis (if reached) to control the study type I error rate (66), but all confidence intervals will remain two-sided, 95% intervals.

### **Outline of statistical analysis**

The main aim of the statistical analysis will be to establish whether there is any benefit of hypertonic saline solution in the treatment of acute bronchiolitis in infants. The primary outcome for this trial is the time to 'fit to discharge'. This will be measured at 6 hourly intervals, with the first evaluation at time of randomisation. Secondary outcomes include:

- Actual time until discharge, measured from time of randomisation
- Quality of life of both carer and child, measured at 28 days from randomisation using the ITQoL. It contains 13 dimensions covering both child and parent QoL, each of which is scored from 0 (worst health) to 100 (best health).



- Readmissions, measured as: the percentage of children readmitted at least once within 28 days from randomisation; total amount of time spent in hospital in 28 days post randomisation including both the original episode and readmission time. These will be tabulated by study group and further classified according to whether the readmission was related to the original bronchiolitis or a new presenting complaint.
- Duration of respiratory symptoms post discharge and within 28 days from randomisation.

The primary outcome variable is time to 'fit for discharge'. This can be regarded as a survival time and methods appropriate to survival data will be used to analyse these data as these can take account of censoring. Initially Kaplan-Meier survival curves will be computed and formally compared using the log-rank test. In addition, depending upon the need to adjust for covariates, a cox-proportional hazards regression model will be used. The proportionality of the hazards will be assessed using time-dependent covariates and scaled Schoenfeld residuals (67).

The analysis of actual time to discharge will be similar to the primary outcome measure time to 'fit to discharge'. For other secondary outcomes the statistical method appropriate to the data type will be used. For example, readmission rate will be treated as a binary outcome; although it is possible that children could be readmitted multiple times due to their single episode of bronchiolitis, it is much more likely that they will be readmitted just once. Thus the percentage of children readmitted at least once will be calculated by study group and compared, initially with a Fisher's exact test, and if there is a need to adjust for covariates, using a logistic regression model. Each of the 13 dimensions of the ITQoL will be tabulated and examined for differences between treatment groups, initially using a t-test. Where the assumptions underlying the t-test do not hold, a Mann-Whitney U test will be used. Where there is a need to adjust for covariates the relationship between the groups for each dimension of the ITQoL scale will also be compared using a linear regression model.

The primary analysis of efficacy will be by intention to treat, that is, it will be performed according to the groups that patients were allocated to, irrespective of whether they remained in these groups. As a sensitivity analysis a per protocol analysis will be performed for the main outcomes. Where individuals are lost to follow-up or data are missing, the reason for missing data will be investigated and where appropriate sensitivity analyses will be conducted to evaluate the impact of the missing data.

In addition to the intention to treat and per protocol analyses detailed above, the dataset will be examined for safety issues. Whilst no formal statistical analysis is planned the adverse event rates will be examined according to the last treatment received. This will include examining differences by seriousness (non-serious/serious) and whether they are considered to be related to treatment (unrelated/potentially related/related).

It is of interest to investigate outcomes between those infants with human respiratory syncytial virus (RSV) infection and those with acute bronchiolitis due to one of the many other respiratory viruses that can cause the same clinical phenotype (non-RSV). There is currently no evidence about whether the response to treatment would differ between these two patient groups and if so what the likely

magnitude might be. Thus, results will also be reported separately for the RVS and non-RSV groups in order to provide information for a power calculation for a future study, investigating the relative efficacy of nebulised hypertonic saline for RSV compared to non-RSV patients.

### **Sample size calculation**

Based on a current time to discharge criteria of around 3 days, we feel that a 25% reduction would be the minimum clinically significant effect and this is the magnitude of the effect observed in previous studies[24]. Using Hospital Episode Statistics (HES) data relating to the median and mean length of stay (LOS), and assuming a log-normal distribution, the standard deviation (SD) is estimated at 32 hours. Whilst a similar, or smaller, SD is expected for our primary outcome measure, a slightly inflated SD of 46 hours is used due to uncertainties over its derivation here. In order to have a 90% power to detect a 25% difference in time to meeting discharge criteria, the study will need 139 patients per group at a two-sided alpha level of 5%. The dropout rate is thought to be negligible for the analysis of the primary outcome measure and therefore a conservative estimate of sample size is 150 patients per group. It is anticipated that up to nine centres will recruit patients into the study. A target has been set of 25 participants for District General hospitals and 40 participants for Teaching hospitals.

## **9.0 ECONOMIC EVALUATION**

A cost-utility analysis (CUA) will be undertaken from the NHS perspective with a time frame of 28 days post-randomisation. Given the difficulties of measuring utilities in the very young, we will supplement the CUA with a cost-consequences analysis which presents the secondary clinical outcome measures alongside costs to allow a more qualitative assessment of cost-effectiveness.

Resource use information will be collected covering length of stay by type of ward, readmissions and other primary care (e.g. general practitioner or emergency department visits). These will be costed using the most recent versions of NHS Reference Costs and the Unit Costs of Health and Social Care publication produced by the Personal Social Services Care Unit (PSSRU). Quality adjusted life years (QALYs) will be based on population norms with decrements proportional to the time spent in hospital over the follow-up period. The utility decrement for a day in hospital will be derived from a recently published valuation study relating to hospitalisation in paediatric populations [68].

Costs and QALYs will be described using non-parametric permutation tests that allow robust comparisons of the means in the presence of non-normal data. Paired cost and QALY data will then be bootstrapped and plotted on the cost-effectiveness plane. The focus of the economic analysis will be the resultant cost-effectiveness acceptability curve and the probability that the intervention will be cost-effective at £20,000 per QALY. Sensitivity analysis will examine the degree to which different hospital costs impact on the results in order to assess the generalisability of the results. One-way sensitivity analysis will also be undertaken using other utility estimates from a literature review that will be undertaken in the final six months of the study.

## 10.0 SAFETY ASSESSMENTS

Clinical staff will undertake ongoing monitoring as per usual clinical care. The Research Nurse will undertake retrospective safety assessments.

Serious Adverse Events (SAEs) will be reported in accordance with the Clinical Trials Research Unit (CTRU) Standard Operating Procedure PM004 Adverse Events & Serious Adverse Events. The Principal Investigator (PI), or delegated investigator, is responsible for reporting all SAEs to both the Sponsor and CTRU in Sheffield by fax within 24 hours of being alerted to the SAE.

The Sponsor and CTRU are responsible for assessing the seriousness and reporting to relevant regulatory bodies, where appropriate.

If an SAE is categorised by the PI/CI as related and unexpected the REC must be informed within 15 days of the Sponsor and CTRU being alerted. This is the responsibility of the Trial Manager at the CTRU, or delegated person in their absence. This should be reported to the REC using the Safety report form for non-CTIMPs (Clinical Trial of Investigational Medicinal Products).

Site trial staff and delegated NHS staff are responsible for recording all Adverse Events (AEs) that are reported by the participant and making them known to the PI. AEs will be recorded on the Case Report Form and database but do not need to be reported by fax to the Sponsor and CTRU. AEs and SAEs will be reported regularly in data reports to the oversight committees.

Admission per se of a study participant to the HDU and/or ICU as a result of normal clinical diagnosis of acute bronchiolitis will be reported as an expected event not as an SAE.

### **Monitoring**

The trial will be monitored and audited in accordance with the monitoring Standard Operating Procedures of the CRF and the CTRU. All trial related documents will be made available on request for monitoring and audits by the sponsor and the relevant Research Ethics Committee. The detailed data management and data quality issues will be set out by the trial manager and CTRU database manager in a data management and monitoring protocol in line with SOP DM009 Data Management & Monitoring Protocol.

Three committees will be established to govern the conduct of the trial:

- Trial Steering Committee (TSC)
- Data Monitoring and Ethics Committee (DMEC)
- Trial Management Group (TMG)

A Trial Steering Committee will be established which will include an independent chair, Professor Jonathan Grigg, who is a clinician with research and clinical experience in the field of respiratory illness in early childhood. Prof. Grigg has undertaken intervention studies in pre-school children with acute SABRE protocol v8.0, 04 June 2013

wheeze [there are no other UK centres that have undertaken interventional studies in patients with acute bronchiolitis other than those included in this proposal].

The TSC's responsibilities will include supervising the progress of the trial and ensuring adherence to protocol. The TSC can prematurely close the trial. It will act in accordance with CTRU SOP GOV002 Trial Steering Committee.

An independent Data Monitoring and Ethics Committee will consist of an independent statistician, and two independent experts. Its responsibilities will include reviewing the trial data at regular intervals and implementing stopping rules in accordance with MRC guidance. The DMEC can recommend premature closure of the trial to the TSC. It will act in accordance with CTRU SOP GOV003 Data Monitoring and Ethics Committee.

The Trial Management Group will include the Chief Investigator, Co-applicants, Principal Investigators, CTRU Assistant Director, Trial Manager, Research Nurses, Statistician, Health Economist and a service representative. It will oversee the implementation of the trial and act in accordance with CTRU SOP GOV001 Trial Management Group.

## **11.0 ETHICAL CONSIDERATIONS**

The principal ethical consideration is that the subject group are unable to provide their own consent but this is an issue for all paediatric studies involving infants and young children. For this study there are no known risks associated with the intervention and the participating units are very familiar with the ethical challenges in this population.

None of the previous studies using this intervention have noted any significant adverse events attributable to the hypertonic saline, although nebulisation can be associated with crying and the saline may cause coughing.

There may be a small chance that participants are involved in other research studies and this question will be asked during the informed consent process. Should the investigating team feel it would be inappropriate to include them in the study they will be excluded on this basis.

### *Ethics and R&D approval*

The trial will be conducted subject to a Research Ethics Committee favourable opinion, including any provisions for Site Specific Assessment, and local Research and Development approval.

It will be conducted in accordance with ICH Harmonised Tripartite Guidelines for Good Clinical Practice.

## **12.0 FINANCE AND INDEMNITY**

Research funding has been obtained from the NIHR Health Technology Assessment programme to support individual research sites as well as trial management. Applications will be sought for local service support and commissioning costs.

This is an NHS sponsored study. For NHS sponsored research HSG (96) 48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

### 13.0 REPORTING AND DISSEMINATION

The results of the trial will be disseminated in peer reviewed scientific journals, clinical and academic conferences and on the study website. No report, either verbal or written may be made without the approval of both the TMG and TSC.

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Document History

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2	<b>General Information</b>	
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