Cedar
Healthcare Technology Research Centre

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board

Study Protocol

PREADAPT-Sepsis

Full title: PRocess Evaluation of the ADAPT-Sepsis trial (PREADAPT-Sepsis): Factors influencing implementation of biomarker guidance for antibiotic prescribing decisions in sepsis

Version:	2.0
Date:	28 June 2022
Chief Investigator:	Ruth Louise Poole, Senior Healthcare Evaluation Scientist, Cedar, Cardiff & Vale UHB
Sponsor:	Cardiff & Vale University Local Health Board

FULL/LONG TITLE OF THE STUDY

PRocess Evaluation of the ADAPT-Sepsis trial (PREADAPT-Sepsis): Factors influencing implementation of biomarker guidance for antibiotic prescribing decisions in sepsis

SHORT STUDY TITLE / ACRONYM

PRocess Evaluation of the ADAPT-Sepsis trial (PREADAPT-Sepsis)

This protocol has regard for the Health Research Authority guidance and order of content

PROTOCOL VERSION NUMBER AND DATE

Protocol amendments must be submitted to the Sponsor for approval prior to submission to regulatory authorities.

Version	Produced by	Amendments	Date
1.2	Ruth Poole	Edited text (section 6.2). Removed specific PIS/ICF version numbers. Changed ward nurse to ICU/ward nurse, and QuIET+ to QuIET throughout. Updated planned study period and version numbering; signed. This version was approved for use, but not implemented.	16/11/2018
2.0	Ruth Poole	The start of the study has been delayed, and no participants have yet been recruited. The main change being reported in this amendment is the recognition that this is a "single site, self-sponsored" study, rather than having multiple participating sites. Other updates have been made to study documents to reflect minor changes to the study design, particularly to allow for remote communications in the context of the Covid-19 pandemic. Potential interviewees will be selected from NHS staff who volunteer to provide their contact details in the QuIET questionnaire, or via the Cedar website. The QuIET questionnaire has been moved from Online Surveys to MS Forms, to align with local information governance requirements. Finally, a decision has been made that no trial data (except that which is publicly available) will be shared with the process evaluation team. The changes have been discussed with the CI of the associated trial and the trial management team. There are no significant resource implications.	28/06/2022

RESEARCH REFERENCE NUMBERS

IRAS Number:	232570
ResearchRegistry.com ID:	ResearchRegistry4244
SPONSORS Number:	Cardiff & Vale UHB R&D reference 18/JUL/7475
FUNDERS Number:	NICE MTEP project number RX127
Cedar reference:	CED113

SIGNATURE PAGE

I, the undersigned, agree to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirements.

I agree to ensure that any confidential information processed during the study will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that:

- I will make the summarised findings of the study publically available through publication or other dissemination tools without any unnecessary delay
- an honest accurate account of the study will be given
- any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator (PREADAPT-Sepsis)

Signature:  **Date:** 28 June 2022

Name: Ruth Louise Poole

CONTENTS

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FUNDING AND SUPPORT IN KIND

FUNDERS	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Intensive Care Foundation	£14,993 received in the form of a New Investigator Award.
National Institute for Health and Care Excellence (NICE)	Funding provided to Cedar as part of its research facilitation role in the NICE Medical Technologies Evaluation Programme. Excludes funding for direct research activities.

ROLE OF STUDY SPONSOR AND FUNDER

The Chief Investigator (a representative of the study Sponsor) is the first author of the protocol and has overall responsibility for its content. Subsequent iterations have been shared with collaborators for discussion and refinement of the content.

Cardiff and Vale University Health Board acts as Sponsor, fulfilling this role according to the principles of Good Clinical Practice. This organisation assumes overall responsibility for the initiation and management of the PREADAPT-Sepsis process evaluation study. It has overall responsibility for study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. It does not assume responsibility for the associated ADAPT-Sepsis randomised controlled trial, which is sponsored by the University of Manchester.

The PREADAPT-Sepsis process evaluation study is co-funded by the Intensive Care Foundation, and the National Institute for Health and Care Excellence (NICE). Both organisations have reviewed the initial draft protocol and had the opportunity to comment. Representatives of NICE and individual members of the Intensive Care Society (ICS) have had opportunities to input into study design, and will receive ongoing information about the study conduct. They may be involved in the interpretation of results, and are likely to be invited to contribute to manuscripts and/or conference presentations. Final decisions (those which relate specifically to PREADAPT-Sepsis rather than ADAPT-Sepsis) will be made at the discretion of the Chief Investigator, or delegated (appropriately trained) representatives at Cedar.

STUDY SUMMARY

Study Title	Factors influencing implementation of biomarker guidance for antibiotic prescribing decisions in sepsis
Study Design	Mixed methods process evaluation (implementation) study
Study Participants	Staff at NHS hospitals involved in the delivery of the ADAPT-Sepsis randomised controlled trial
Planned Sample Size	Data collection from up to 30 NHS hospitals; with approximately 12-15 interview participants
Planned Study Period	Survey and interviews with staff participants will take place between 01 July 2022 and 31 January 2024. Reporting is expected to be completed by 31 July 2024.
Main Research Questions/Aims	1. What are the barriers and facilitators affecting implementation of biomarker-guided antibiotic prescribing protocols for management of sepsis in NHS secondary care? 2. What factors influence secondary care clinician adherence to biomarker-guided antibiotic prescribing protocols for management of sepsis in the UK NHS? 3. Which contextual factors are associated (positively or negatively) with implementation outcomes and trial outcomes?
Key Words	Outcome and Process Assessment (Health Care); Clinical Decision-Making; Sepsis; Anti-Bacterial Agents; Procalcitonin; Implementation

LAY SUMMARY

Procalcitonin and C-reactive protein are biomarkers (natural indicators of illness) found in the blood of people exposed to bacterial infection. Levels are high in people with severe infection (sepsis), but reduce with effective antibiotic treatment. Testing biomarker levels may help to guide the length of antibiotic treatment needed. The prescribed duration needs to be long enough to treat the infection, but if treatment is prolonged it could contribute to the development of antimicrobial resistance (which reduces the effectiveness of antibiotics). A randomised controlled trial (ADAPT-Sepsis) will find out whether using biomarkers to guide antibiotic duration is effective and safe for patients when compared with standard care. Plans for the trial are detailed in a separate protocol.

The trial will identify which intervention (if any) was most effective. A process evaluation is a research method which adds information to help understand *why* a complex intervention was effective or not, and why it may have different outcomes in varying circumstances. PREADAPT-Sepsis is a process evaluation which will find out extra information from the hospitals and staff involved in the ADAPT-Sepsis trial. It aims to find out what factors influence antibiotic prescribing decisions, and what role biomarkers play. Trial staff will be invited to complete questionnaires and to participate in interviews.

At the end of the study, the results of the trial will be combined with the process evaluation findings. The overall results will help us to understand which type of test is most effective, and what approaches can be taken by NHS teams to successfully implement biomarker testing within their local settings.

STUDY FLOW CHART

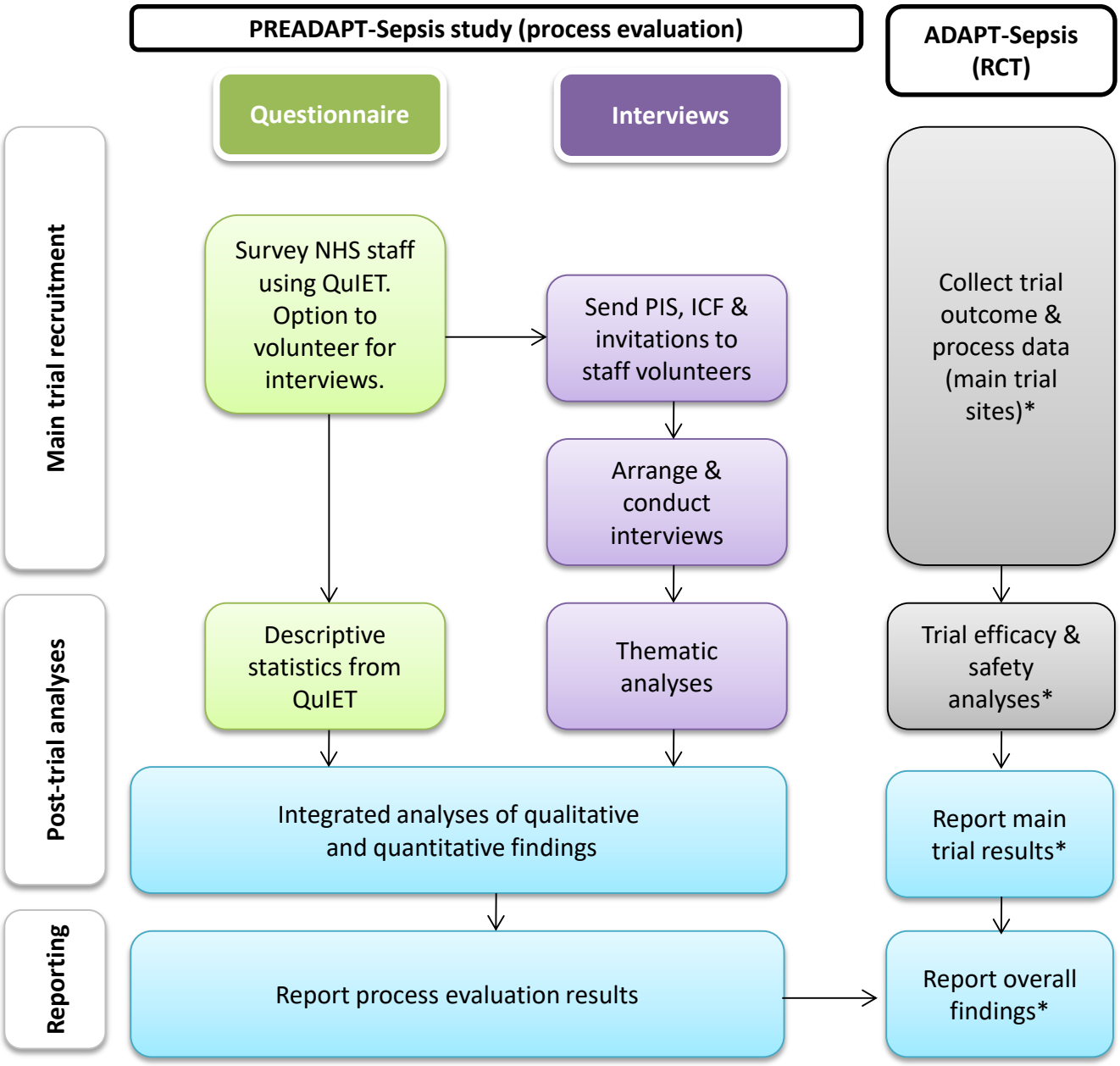

Figure 1. Study flow chart. ICF: Informed Consent Form; QuIET: Quantitative Implementation Evaluation Tool; PIS: Participant Information Sheet.

*Activities led by Warwick Clinical Trials Unit.

1 BACKGROUND

1.1 The ADAPT-Sepsis Trial

This study has designed to be complementary to the ADAPT-Sepsis randomised clinical trial. ADAPT-Sepsis is an important UK-wide multicentre randomised controlled trial (see table 1).

Table 1. Overview of the ADAPT-Sepsis randomised controlled trial.

Design	Multicentre UK-wide 3-arm pragmatic RCT with internal pilot. 30+ sites, estimated sample n=2760
Chief Investigator	Professor Paul Dark
Sponsor	University of Manchester
NHS Contractor	Salford Royal NHS Foundation Trust
Trials Unit	Warwick Clinical Trials Unit (CTU)
Funder	National Institute for Health Research (NIHR) (HTA reference 15-99-02)
Population	Hospitalised adults with sepsis
Intervention arms	Biomarker-guided (procalcitonin or C-reactive protein) decisions on antibiotic duration + standard care
Comparator arm	Standard care
Outcomes	Effectiveness (antibiotic duration), safety, resource use
Registration	ISRCTN47473244

To understand the PREADAPT-Sepsis process evaluation, it is important to first understand the background to the ADAPT-Sepsis trial. In brief:

- Sepsis is a life-threatening condition which can be difficult to diagnose, yet which requires prompt treatment.
- Antibiotic treatment is started within 24 hours of presentation, and a blood sample is sent to a laboratory for microbiological analysis.
- Overuse of antibiotics leads the development of treatment-resistant micro-organisms, so it is important for treatment to not continue longer than necessary. Historically, optimum treatment duration has been based on expert opinion rather than robust evaluation of evidence (Albrich and Harbrath, 2015).
- Laboratory tests may or may not include checking the levels of biomarkers (such as C-reactive protein and/or procalcitonin), which indicate how the body is responding to bacterial infection and to antibiotic treatment.
- The National Institute of Health and Care Excellence has recommended research into the comparative effectiveness of biomarkers to inform prescribing decisions in patients with suspected sepsis (NICE, 2015).
- The trial aims to determine whether a treatment protocol based on monitoring biomarkers for bacterial infection (C-reactive protein and procalcitonin) allows a safe reduction in the duration of antibiotic therapy in hospitalised adult patients with sepsis.
- The trial will provide evidence of the relative effectiveness of three approaches:

    - Using C-reactive protein biomarker testing to inform prescribing decisions
    - Using procalcitonin biomarker testing to inform prescribing decisions
    - Making prescribing decisions according to local standard care practice.
- In all three trial arms, those making prescribing decisions are expected to also use their clinical judgement, which in some situations might be counter to advice issued by the laboratory (which may be described as 'non-adherence').

Upon conclusion of the trial, it should be possible to identify which (if any) of the three approaches is most effective in reducing unnecessary antibiotic use.

1.2 The PREADAPT-Sepsis process evaluation

Previously published trials of procalcitonin-guided antibiotic prescribing were conducted outside the UK. These trials report varying levels of success in reducing unnecessary antibiotic exposure (Albrich and Harbarth, 2015; Westwood et al., 2015). Similarly, the extent to which clinicians comply with biomarker-guided recommendations is variable, with reported adherence being as low as 44% in some circumstances (de Jong et al., 2016).

The National Institute of Health and Care Excellence is interested to learn whether the reported benefits of procalcitonin-guided treatment will translate to the UK context (NICE, 2015). Guideline adherence and prescribing decision-making is influenced by contextual and behavioural factors (such as local policies, social hierarchies, continuity of care, or attitude to risk) (Public Health England, 2015). Little UK evidence is available to indicate adherence to biomarker-guided protocols for managing bacterial sepsis (including reasons for overriding the advice), and broader issues relating to implementation of such algorithms.

The ADAPT-Sepsis trial provides a valuable opportunity to explore some of these issues in relation to the implementation of biomarker-guided protocols when treating adults with suspected sepsis in NHS hospitals.

2 RATIONALE

This will be the first study to prospectively investigate the barriers and facilitators to implementation of both procalcitonin-guided and C-reactive protein-guided prescribing for sepsis in the context of a large multicentre UK trial. It can be helpful to identify and understand the complex interactions between influential factors which might influence clinicians' behaviour, so that barriers to adoption can be anticipated and addressed (Parker and Mattick, 2016). It has been suggested that any hospital using procalcitonin-guided algorithms should monitor the extent to which clinicians adhere to the recommendations, and factors influencing these decisions at a local level (Ammar et al. 2017). Research in this area could inform successful implementation elsewhere, avoid potential negative health outcomes for individuals and society, and reduce economic waste associated with inappropriate non-compliance.

Frontline clinical teams will also be armed with additional knowledge about which circumstances (and in which patients) these tests are of most value, potentially increasing their confidence in making appropriate decisions. The wider implications are that patients will receive clinical care tailored to their needs, whilst more responsible use of antibiotics in the NHS will help to combat antimicrobial resistance.

3 THEORETICAL FRAMEWORKS

Two main frameworks help to conceptualise the methodological approach being taken in PREADAPT-Sepsis. Firstly, Medical Research Council (MRC) process evaluation guidance illustrates how relationships between three core areas can impact outcomes: how the intervention is delivered, its mechanism of action, and the context in which it is deployed (Moore et al., 2015). In PREADAPT-Sepsis, the intervention is considered to be biomarker-guided prescribing. How it is delivered includes whether or not the prescriber adheres to the biomarker-guided protocol (known as 'fidelity' in this model). Context is multifaceted, and can include the clinical setting, population demographics, and local cultural beliefs or attitudes. The red text and arrows in figure 2 show the relationships of particular interest in this study.

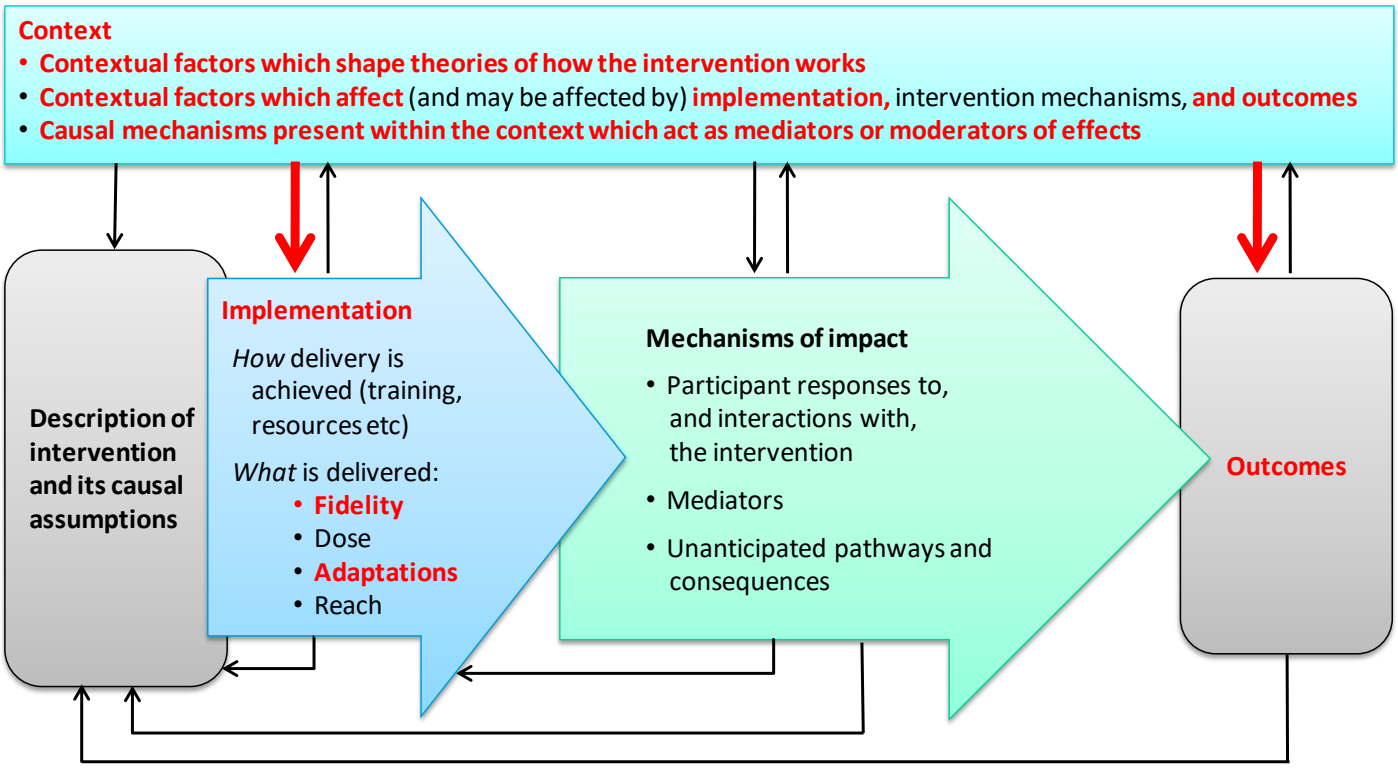

Figure 2. MRC Framework for Process Evaluation of Complex Interventions (Adapted from Moore et al., 2015). PREADAPT-Sepsis focuses on the influence of contextual factors on implementation fidelity, and the influence of contextual factors on intervention outcomes. These relationships are highlighted in bold red text.

The Consolidated Framework for Implementation Research (CFIR) is a well-established implementation framework which is closely aligned with the aims of PREADAPT-Sepsis, and provides a helpful basis for evaluation. CFIR is a product of previously published theories, bringing together a number of constructs to explain what works, where, and why, in different contexts. Damshröder et al. (2009) encourage tailoring of the framework to suit the setting and scenario. Because prescribing decisions are a key area of interest in PREADAPT-Sepsis, the following CFIR domains and constructs have been selected for particular scrutiny:

- **Outer setting** (patient needs & resources, peer pressure, external policies)
- **Inner setting** (social architecture/hierarchies, culture, climate)
- **Characteristics of the individuals** involved (knowledge and beliefs about the intervention, self-efficacy/autonomy, stage of change/experience of the intervention)

4 RESEARCH QUESTIONS

The main overall aim is to investigate factors influencing implementation of biomarker-guided antibiotic prescribing in adults with suspected sepsis.

Specific research questions which arose from our exploration of context, identification of evidence gaps, and hypothesised theory, were:

1) What are the barriers and facilitators affecting implementation of biomarker-guided antibiotic prescribing protocols for management of sepsis in NHS secondary care?
2) What factors influence secondary care clinician adherence to biomarker-guided antibiotic prescribing protocols for management of sepsis in the UK NHS?
3) Which contextual factors are associated (positively or negatively) with implementation outcomes and trial outcomes?

5 METHODS OF DATA COLLECTION

There are three main streams of data collection and analysis. These are shown in the flow chart on page ix, which is intended for reference alongside sections 5 and 6 of this protocol.

The three streams are:

1) Quantitative data (questionnaires) – relating to organisational characteristics, culture and climate
2) Qualitative data – identifying themes arising from semi-structured interviews with staff
3) Trial & process data – for main ADAPT-Sepsis trial effectiveness, fidelity/adherence, safety and economic analyses.

Whilst the trial was being piloted, face and content validation of the QuIET (Quantitative Implementation Evaluation Tool) was carried out with the involvement of a small number of clinicians.

5.1 Quantitative questionnaire data collection

The Quantitative Implementation Evaluation Tool (QuIET) is a questionnaire which was designed using Microsoft Forms, and is based upon CFIR domains and constructs (Damshröder et al., 2009). The aim is to collect data which reflects the characteristics, attitudes and implementation context from individuals, for summarisation at an organisational level. Respondents are invited to rate the strength of their agreement with a list of individual statements using a Likert scale. There are also opportunities to add free text comments to elaborate on responses. A link to the survey will be sent to each of the ADAPT-Sepsis trial sites, with an invitation to all eligible staff to return anonymous submissions. Warwick CTU will facilitate distribution of these questionnaire invitations to participating hospitals via email. Hard copies of the questionnaire are available on request if staff are unable to access the online version, and a Welsh translation is also available.

5.3 Qualitative interview data collection

Rich qualitative data will be collected through interviews with selected members of NHS staff, but outside of their professional capacity (ie not on NHS time or at an NHS site). Interviews will be carried out remotely using Microsoft Teams. Whenever possible, the interviews will be led by the PREADAPT-Sepsis CI. If necessary, this task will be delegated to another Cedar researcher (provided they have appropriate experience or training in carrying out qualitative interviews). The interviewer will seek permission from the interviewee to record the discussion through the recording function in Microsoft

Teams. The interviewer will also make field notes to record their observations during and after the interview if required.

A semi-structured interview topic guide has been prepared. CFIR domains and constructs (Damschrőder et al., 2009) have informed deductive prompts in the interview topic guide, to be supplemented by probing (inductive) questions as guided by participant responses. The iterative nature of the qualitative analyses allows for adaptation of the topic guide as the study progresses.

5.4 ADAPT-Sepsis trial and process data collection

The third stream is the responsibility of the ADAPT-Sepsis trial team – Professor Paul Dark (trial Chief Investigator), the University of Manchester (trial Sponsor) and Warwick Clinical Trials Unit (sub-contracted by the trial Sponsor to run the trial). Methods for trial data collection and analysis are documented within the main ADAPT-Sepsis trial protocol, and are not covered in detail here.

Process data will be regularly collected by Warwick CTU to monitor ADAPT-Sepsis trial progress with respect to recruitment rates, and shared with the PREADAPT-Sepsis researchers though updates delivered in the Trial Management Group (TMG) and the NIHR Open Data Platform. Outcomes of the trial interventions will be shared at the end of the study. No individual patient-level data will be shared with the PREADAPT-Sepsis research team.

6 METHODS OF DATA ANALYSIS

Data analysis activities correspond with the three project streams:

1) Quantitative data – descriptive summary of QuIET questionnaire responses
2) Qualitative data – thematic analysis based on interview transcripts
3) Trial data – final integrated analyses, combining questionnaire and interview data, considered in the context of the main trial outcomes.

6.1 QuIET analysis

Analysis of QuIET questionnaire data will identify which CFIR constructs generated the most heterogeneous responses. These will inform revisions of the interview topic guide, to allow these differences to be explored further during the qualitative interviews.

In the final report, constructs from the QuIET questionnaire will be reported in summary form, indicating the range of responses and the type of variation observed. These descriptive statistics will provide an overall picture of organisational characteristics and cultural context, including baseline attitudes towards implementation of the intervention.

6.3 Thematic analysis of qualitative interview data

Factors which influence clinical decision-making/adherence to biomarker guidance, and barriers and facilitators to implementation will be identified via thematic analysis of interview transcripts. The iterative nature of the qualitative data collection will enable the further exploration of themes arising from earlier data collection. Collecting data from hospitals experiencing differing stages of implementation may reveal emerging changes over time, progressive experiences of the intervention, and unanticipated or complex causal pathways.

Thematic analyses will be carried out by the Chief Investigator or qualitative researcher with delegated responsibilities prior to publication of trial results. Hypotheses can then be generated about the mechanisms of impact (the potential influence of different factors on trial outcomes) and contextual moderators.

6.4 Final integrated analyses

The analytic teams for the trial (Warwick CTU) and for the process evaluation (Cedar) will produce results independently. With the exception of process data (such as recruitment rates), findings will only be shared between teams once the main trial results are available and qualitative data analyses are complete. At this final stage of analysis, trial results (relating to clinical outcomes) will be examined alongside PREADAPT-Sepsis findings (both quantitative and qualitative).

7 SAMPLING AND RECRUITMENT

7.1 Eligibility Criteria

The study will collect quantitative data from questionnaires issued to staff working on the ADAPT-Sepsis trial. Eligibility criteria for sites participating in the trial (and for patients being recruited to the trial) are defined in separate documentation specifically relating to ADAPT-Sepsis. Qualitative data will be collected from a sample of participating NHS staff who work at trial sites. This section focuses on the methods used to identify these individuals.

Inclusion criteria

- Member of staff involved in implementation or delivery of the ADAPT-Sepsis trial at an NHS site.

7.2 Sampling

7.2.1 Sampling technique and identification

The qualitative study stream will aim to use purposive diversity sampling for maximum variation, but will be limited to NHS staff who volunteer to provide their contact details through the Cedar website or when responding to the QuIET questionnaire. Selection of interviewees will be informed by a theoretical sampling framework (tables 3 and 4). We hope to recruit individuals representing a range of roles within the trial delivery teams, and from organisations with differing recruitment rates. Sampling may be further influenced by the findings of the QuIET questionnaire, specifically targetting outliers (where questionnaire responses suggest local variation in approach or behaviour).

Interviews will be conducted remotely using Microsoft Teams. Initially we aim to interview 12 individuals in total. If key themes continue to emerge after the first 12 interviews, further interviews will be arranged. This design is based on the recommendations of Francis et al. (2010).

Table 3. Theoretical sampling framework for qualitative interviews. Adapted from CFIR website (2014).

Axis of diversity	Operationalised selection criteria	Rationale for operationalisation
Site recruitment rate	Two groups according to recruitment rate: (1) High recruitment (2) Low recruitment	To elicit local contextual (culture, climate) reasons for different levels of recruitment
Role in organisation	Five groups: (1) Consultant/senior doctor (2) Junior doctor (FY1/FY2) (3) Microbiologist or pharmacist (4) Research nurse (5) ICU/ward nurse	Perceptions of the intervention may vary by role

Table 4. Target sampling matrix for initial interviews. Adapted from CFIR website (2014). Further interviews may be conducted subject to adequate identification of key themes.

	Initial sample (n=12)				
	Consultant/ senior doctor	**Junior doctor**	**Microbiologist or pharmacist**	**Research Nurse**	**ICU/ward Nurse**
High site recruitment	2	1	1	1	1
Low site recruitment	2	1	1	1	1

7.2.2 Consent

There are two circumstances in which the principle of consent could be relevant within this study:

1. Collection of questionnaire data from clinical staff
2. Participation of NHS staff in qualitative interviews.

The Health Research Authority encourages provision of participant information that is proportionate to:

- the complexity of research,
- the risks, burdens and possible benefits to participants
- related ethical issues.

This process evaluation is considered to be low risk. The proposed methods for obtaining consent are:

1. **Questionnaire:** Questionnaire respondents will not be required to submit personal identifiable information, but there will be an option to submit contact details (name, email address, telephone number) if they are willing to be contacted by Cedar. A short introductory paragraph will explain the purpose of the process evaluation, why they are being asked to complete the questionnaire, how the information collected will be used and stored, and how the findings will be made available. Contact details for the research team will be made available in case of any questions. Respondents will be required to actively acknowledge that they have read and accepted the introductory paragraph before they are able to access the main questions.

2. **Qualitative interviews:** Potential interviewees will be identified from those questionnaire respondents who opted to provide their contact details to Cedar. They will be sent a participant information sheet (PIS) and informed consent form (ICF) when planning a suitable date and time for an interview. There will also be an option for people to volunteer for interviews through a page on the Cedar website; respondents will be directed to read the PIS and ICF before deciding whether they wish to provide their contact details through a link to MS Forms.

   Immediately prior to the interview, the interviewer will go through the PIS, ask the participant to confirm their name, job role, and NHS employer, and ask the participant (NHS staff) if they are willing to consent to the interview. Verbal consent from the participant will be recorded as part of the video recording of the interview in Microsoft Teams. This process will be documented by the interviewer who will sign and date the ICF on behalf of the participant.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

A project risk register has been populated, and is maintained by the Chief Investigator and Cedar researchers. Risks, issues and opportunities are regularly reviewed at internal project progress meetings. Monitoring and auditing of study conduct will be proportionate to the low-risk nature of this process evaluation, in accordance with local policies and procedures.

Data collection for PREADAPT-Sepsis will primarily be from clinicians who work at the ADAPT-Sepsis trial sites. There will be no direct benefit to participants. There is a small potential risk of disclosure of sensitive information by members of NHS staff, about themselves or others. To mitigate this risk, prior to starting interviews or questionnaires, these participants will be requested not to disclose such issues, and will be informed of potential consequences. If such a disclosure occurs, it should be reported to the Chief Investigator (of the PREADAPT-Sepsis process evaluation), who will inform the Chief Investigator for the ADAPT-Sepsis trial and/or the trial Sponsor as appropriate. The QuIET online survey was created using the Microsoft Forms application (accessed via the NHS), and only intends to collect anonymised data, though there is a small risk of voluntary disclosure of personal identifiable data.

PREADAPT-Sepsis will involve no direct contact with patients, and no additional risks to the patient-participants of the ADAPT-Sepsis trial. All data processing will be carried out in adherence with relevant data protection legislation.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Based on guidance from the following sources, it is expected that the PREADAPT-Sepsis project is likely to fall into the category of a “non-REC” research project:

- IRAS application guidance (project filter question 4)
- Governance Arrangements for Research Ethics Committees (2.3.13 and 2.3.10)
- Updated Governance Arrangements for Research Ethics Committees (1.3.3 and 2.3.14)
- Direct contact with Health and Care Research Wales
- Direct contact with the manager of the South Central – Oxford C REC (which provided a favourable opinion for the ADAPT-Sepsis trial).

The main reasoning for this conclusion is that REC review is not normally required for research involving NHS staff recruited as research participants by virtue of their professional role.

Before enrolment of participants into the study, the Chief Investigator or designee will ensure that appropriate approvals are in place. An application will be submitted to Health and Care Research

Wales through the Integrated Research Application System (IRAS). This organisation will advise if they consider REC review to be necessary and, if required, a favourable opinion will be sought from a REC before commencement of research activities. The Chief Investigator will adhere to reporting requirements as advised by Health and Care Research Wales.

8.2.1 Amendments

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. Amendments should be documented on page ii of this protocol.

If the sponsor wishes to make an amendment to their IRAS application, Health and Care Research Wales must be notified; REC review may also be required.

Due to the close relationship between the two studies, the PREADAPT-Sepsis sponsor will inform the CI of the ADAPT-Sepsis trial of any substantial amendments. Substantial amendments should also be notified to study funders (NICE and the Intensive Care Society). It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial.

8.3 Peer review

The National Institute for Health and Care Excellence (NICE) reviewed the original study plans and provided feedback. An overview of the study protocol was submitted for peer review to the Intensive Care Society (ICS) in abstract form, and an oral presentation was made to members of the Society in attendance at the UK Critical Care Research Forum (UKCCRF) in June 2017. The study also received peer review as part of the funding application to the Intensive Care Foundation.

PREADAPT-Sepsis is anticipated to have met the eligibility criteria for inclusion on the Health and Social Care Portfolio, as follows:

- The Intensive Care Society (via its charitable branch, the Intensive Care Foundation) has non-commercial funding status with the National Institute for Health Research (NIHR Non-commercial Partner List, 2017).
- Funding was secured through open competition
- Peer review by the ICS was independent, expert and proportionate.

8.4 Participant Involvement

The subjects of the process evaluation study are NHS site staff involved in the ADAPT-Sepsis trial. The PREADAPT-Sepsis CI is a member of the ADAPT-Sepsis Trial Management Group (TMG), which includes patient/public representatives and trial clinicians. The TMG is aware of the plans for the PREADAPT-Sepsis process evaluation, and has regular opportunities to influence design, interpretation of results, and reporting. Clinical teams participating in the pilot phase of ADAPT-Sepsis were invited to test the QuIET questionnaire, and to provide feedback on its design for validation purposes.

8.5 Protocol compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. Accidental protocol deviations can happen at any time. They must be adequately documented and reported to the Chief Investigator and sponsor immediately. Deviations from the protocol which are

found to frequently recur will require immediate action and could potentially be classified as a serious breach.

8.6 Data protection and patient confidentiality

All investigators and researchers must comply with the requirements of the General Data Protection Regulation EU (2016/679) with regards to the collection, storage, processing and disclosure of personal information. Study data will be stored and processed on secure NHS servers at Cardiff & Vale University Health Board; the data controller for this organisation is the Medical Director. Only Cedar staff and authorised individuals (such as NHS staff providing IT support for Cardiff & Vale UHB) will be granted access to study data.

Personal identifiable data relating to NHS staff will be used only for the purpose of arranging interviews and recording consent, and will be processed according to the sponsor's standard operating procedures and relevant legislation. All reasonable efforts will be made to ensure that neither the audiovisual recordings nor field notes include personal identifiable information of participants.

Participants' rights to access, change or move their information are limited, as the information needs to be managed in specific ways in order for the research to be reliable and accurate. If a participant withdraws from the study, the information about them that has already obtained will be retained, with the exception of their personal identifiable data.

Study data will be archived in accordance with the Cardiff & Vale UHB Archiving of Clinical Trial and Research Study Data Standard Operating Procedure. No personal identifiable data relating to NHS staff will be retained beyond the end of the study.

8.7 Indemnity

With regard to the potential legal liability of the sponsor for harm to participants arising from the design, conduct and management of the research, indemnity is provided through NHS schemes. Researchers with substantive NHS employment contracts designed the research, which is sponsored by an NHS organisation.

In the extremely unlikely event that something does go wrong, and a participant is harmed during the research study, there are no special compensation arrangements. If a participant is harmed and this is due to someone's negligence then they may have grounds for a legal action for compensation against Cardiff and Vale University Health Board, but they may have to pay the legal costs. The normal National Health Service complaints mechanisms will still be available.

8.8 Access to the final study dataset

The full, final study dataset and interview transcripts will only be accessible to Cedar staff (Cardiff & Vale UHB). The full dataset is not expected to be made available for secondary research, due to small sample sizes within subgroups. In accordance with standard measures to prevent statistical disclosure, quantitative data relating to five or fewer individuals will be aggregated or redacted prior to publication. Similarly, full interview transcripts will not be made available to external individuals or organisations due to the possibility of statistical disclosure from these qualitative data.

9 DISSEMINATION POLICY

9.1 Dissemination policy

On completion of data collection for the process evaluation study, data will be analysed and a final report will be prepared. Writing of the final report, manuscript and dissemination of findings is the responsibility of the Chief Investigator. Some of the process evaluation findings may be incorporated into the ADAPT-Sepsis NIHR Health Technology Assessment report, which is the responsibility of Professor Paul Dark (the trial CI).

The final report from PREADAPT-Sepsis will be published on the Cedar website and made available to the ADAPT-Sepsis trial sites for dissemination amongst participating staff. The report will be shared with NICE for consideration when reviewing related guidance (NICE, 2015), and with the Intensive Care Society.

Results from the study will be submitted for publication in a peer-reviewed journal. In addition to submitting an abstract for presentation at the Intensive Care Society's State of the Art Meeting we aim to present this work at one or more conferences, such as the Health Technology Assessment international (HTAi) conference. Articles and abstracts accepted for publication will be referenced on the Cedar website. Such publications and presentations will acknowledge the funders of the research. Publicly available materials may be shared via social media.

Whilst the main aim of this work is to focus on the implementation of biomarker-guided prescribing in sepsis, wider lessons may be learned with implications for intervention theory or methods development. Any substantial contributions of this nature will be shared with an appropriate audience. Furthermore, we hope to explore the potential for knowledge mobilisation and more widespread dissemination of our findings across other NHS sites and the wider research community.

9.2 Authorship eligibility guidelines

For manuscripts intended for publication in peer-reviewed journals, the authorship criteria of the International Committee of Medical Journal Editors (2018) will be followed:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The final ADAPT-Sepsis NIHR Health Technology Assessment report is the responsibility of the trial Sponsor/Chief Investigator.

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