

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC., A SUBSIDIARY OF MERCK & CO., INC., RAHWAY, NJ, U.S.A.

SPONSOR:

Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor)
120 Moorgate, London, United Kingdom, EC2M 6UR

TITLE:

MicroGuide2: A randomized controlled trial of the impact of MicroGuide™ computerized decision support modules on antimicrobial prescribing behaviours and clinical outcomes.

CHIEF INVESTIGATOR:

Dr Philip Scott

PRINCIPAL INVESTIGATORS:

Dr Kieran Hand & Prof Sue Latter

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE: PENDING

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

Version History

Version	Approval Date		Changes
2.4	12-Jan-2021	Original	
2.5	18-Oct-2021	Amendment	<p>Sponsor Contact Information - Research Project Manager Contact Information Updated</p> <p>1.3 Clinical Risk Management - Removed the following text: <i>Horizon Strategic Partners will provide their DCB 0129 documentation when this protocol is submitted for ethics review.</i></p> <p>6. 1.1 Investigator Responsibilities - deleted section of primary data collection as it is replaced with the new template AE reporting language.</p> <p>7.2.3 Limitations - Changed wording to state that each Trust will develop their own decision support modules (DSM) with the support of the study team.</p>

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

Version	Approval Date		Changes
3	See header for approval date	Amendment	<p>Supplier Contact Information - Chief Investigator profile and contact information updated; Director of Research profile information updated</p> <p>Protocol Summary - Supplier's details updated; changed wording to clarify on sample size calculation and redefined study population</p> <p>3.1. Summary of Study Design - Timescales extended due to pandemic impacts.</p> <p>3.2. Study Population - redefined to include all NHS Trusts that use MicroGuide,</p> <p>3.3 Inclusion Criteria - For inclusion criteria: Demonstrating carbapenem class antimicrobial consumption within a middle band for NHS Trusts in England; added wording to <i>optimize study power</i></p> <p>5 Study Flow Chart - Trial Design Overview added</p> <p>6.1.1.1 Protection of Human Subjects - Site recruitment methods expanded.</p> <p>8.3. Sample Size and Power Calculations - changed percentage of change in primary outcomes (from 15% to 20%) and number of Trusts (from 9 to 8) to achieve study power of 80%; study power of 90% has been removed.</p>

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

Table of Contents

VERSION HISTORY 2

TABLE OF CONTENTS 4

SPONSOR CONTACT INFORMATION 7

SUPPLIER CONTACT INFORMATION 7

LIST OF ABBREVIATIONS 8

LIST OF DEFINITIONS 9

PROTOCOL SUMMARY 10

1 BACKGROUND AND RATIONALE 12

 1.1 Background 12

 1.2 Rationale 13

2 OBJECTIVES AND HYPOTHESES 14

 2.1 Primary Objective(s) & Hypothesis(es) 14

 2.2 Secondary Objective(s) & Hypothesis(es) 14

 2.3 Exploratory Objective(s) & Hypothesis(es) 15

3 METHODOLOGY 16

 3.1 Summary of Study Design 16

 3.2 Study Population 16

 3.3 Inclusion Criteria 17

 3.4 Exclusion Criteria 17

4 VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS 18

 4.1 Outcomes 18

 4.2 Covariates 18

 4.3 Exposure 19

5 STUDY FLOW CHART 20

6 STUDY PROCEDURES 21

 6.1 Study Procedures 21

 6.1.1 Administrative Procedures 21

 6.1.1.1 Protection of Human Subjects 21

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

- 6.1.1.2 Quantitative Data 22
- 6.1.1.3 Qualitative Data 22
- 6.1.1.4 App Patterns of Use 24
- 7 SAFETY AND PRODUCT QUALITY COMPLAINT REPORTING AND RELATED PROCEDURES ... 26**
- 7.1 Adverse Event and Product Quality Complaint Reporting 26
 - 7.1.1 INVESTIGATOR RESPONSIBILITY: 26
- 7.2 DEFINITIONS 27
 - 7.2.1 Adverse Event (AE) 27
 - 7.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR) 27
 - 7.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR) 27
 - 7.2.4 Non-serious Adverse Reaction (NSAR) 27
 - 7.2.5 Special Situations 28
 - 7.2.6 Product Quality Complaint (PQC) 28
 - 7.2.7 Malfunction 28
 - 7.2.8 Sponsor's product 28
 - 7.2.9 Causality Assessment 29
- 8 STATISTICAL ANALYSIS PLAN 30**
- 8.1 Statistical Methods 30
 - 8.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest 30
 - 8.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest ... 30
 - 8.1.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest . 30
- 8.2 Bias 31
 - 8.2.1 Methods to Minimize Bias 31
 - 8.2.2 Limitations 31
- 8.3 Sample Size and Power Calculations 32
- 9. ADMINISTRATIVE AND REGULATORY DETAILS 33**
- 9.1 Confidentiality 33
 - 9.1.1 Confidentiality of Data 33
 - 9.1.2 Confidentiality of Study Records 33

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

9.1.3 Confidentiality of Investigator Information..... 33

9.2 Compliance with Financial Disclosure Requirements 34

9.3 Compliance with Law, Audit and Debarment 34

9.4 Quality Management System 35

9.5 Data Management 36

9.6 Institutional Review Board/ Independent Ethics Committees 36

10 PUBLICATIONS 37

11. REFERENCES 38

12 SIGNATURES41

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

Sponsor Contact Information

<p>Dr Mike Allen</p> <p>Regional Medical Advisor MERCK SHARP & DOHME (UK) LIMITED 120 Moorgate London United Kingdom EC2M 6UR 07779 706336</p>	<p>Mrs Amazigom Mayes</p> <p>Senior HTA & EBM Manager MERCK SHARP & DOHME (UK) LIMITED 120 Moorgate London United Kingdom EC2M 6UR 07974 444655</p>
<p>MSc Edita Custic Weguelin</p> <p>Research Project Manager MERCK SHARP & DOHME (UK) LIMITED 120 Moorgate London United Kingdom EC2M 6UR 07887 934711</p>	

Supplier Contact Information

<p>Dr Phillip Scott</p> <p>Programme Director University of Wales Trinity St David Swansea Business School High Street Swansea , SA1 1NE +44 (0)179248100</p>	<p>Prof Anoop Chauhan</p> <p>Director of Research Portsmouth Hospitals University NHS Trust Research Department, Queen Alexandra Hospital, Cosham P036 3LY +44 (0) 23 9228 6000 ext 4042</p>
--	--

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

List of Abbreviations

<i>AE</i>	<i>Adverse Event</i>
<i>PHE</i>	<i>Public Health England</i>
<i>NIHR</i>	<i>National Institute for Health Research</i>
<i>DSM</i>	<i>Decision Support Module</i>
<i>CDS</i>	<i>Clinical Decision Support</i>
<i>IEC</i>	<i>Independent Ethics Committee</i>
<i>DDD</i>	<i>Defined Daily Doses</i>
<i>AMR</i>	<i>Antimicrobial Resistance</i>
<i>RCT</i>	<i>Randomised Controlled Trial</i>
<i>PQC</i>	<i>Product Quality Complaint</i>

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

List of Definitions

Health outcomes

Clinical events or outcomes which may be represented as diagnoses, treatment or procedures (examples include syncope, disease progression or hypoglycemia collected as study endpoints)

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

PROTOCOL SUMMARY

Title	MicroGuide2: A randomized controlled trial of the impact of MicroGuide™ computerized decision support modules on antimicrobial prescribing behaviours and clinical outcomes.
Supplier/Collaborator	Chief Investigator: Dr Philip Scott, Programme Director, University of Wales, Trinity St David, Principal Investigators: Dr Kieran Hand, National Pharmacy and Prescribing Clinical Lead for AMR, NHS England; Prof Sue Latter, School of Health Sciences, University of Southampton.
Rationale	Implementing a decision support module within the MicroGuide application will improve the quality of antimicrobial prescribing resulting in better clinical and microbiological outcomes.
Primary Objective(s)	To determine whether there are statistically significant and clinically significant changes in broad-spectrum antimicrobial prescribing caused by implementation of decision support modules (DSMs) for common infections within the MicroGuide application.
Study Design	Two-arm parallel randomized controlled trial, with NHS Trust as the unit of analysis.
Study Population	Acute NHS Trusts in England that already use MicroGuide (n=107).
Study Duration	Two years (one year intervention period). NHS Trusts randomized to arm A will receive the intervention for twelve months and NHS Trusts randomized to arm B will act as control.
Exposure and Outcome	<p>Exposure = access to MicroGuide decision support modules for five common infections: community-acquired pneumonia; hospital-acquired pneumonia; urinary tract infection; skin and skin structure infection; intra-abdominal infection.</p> <p>Control = continued access to traditional MicroGuide browse format and local guidance.</p> <p>Primary quantitative outcome:</p> <ol style="list-style-type: none"> Carbapenem prescribing volume measured as Defined Daily Doses (DDD) per thousand admissions per NHS Trust aggregated at hospital Trust level. <p>Secondary quantitative outcomes:</p> <ol style="list-style-type: none"> Piperacillin-tazobactam prescribing volume measured as DDD per thousand admissions per NHS Trust aggregated at hospital Trust level. Antimicrobial resistance rates (<i>E. coli</i> resistance to piperacillin-tazobactam). MicroGuide software usage levels and patterns of use. <p>Tertiary quantitative outcomes:</p> <ol style="list-style-type: none"> Aggregate outcome data, excluding diagnosis or antimicrobial, for adult inpatients with coded diagnosis of any of the infections covered by the decision support modules: length-of-stay, 30-day readmission, ICU admission and in-hospital mortality. <p>Qualitative outcomes:</p> <ol style="list-style-type: none"> Opinions of decision support module users at participating hospitals (interviews).
Statistical Methods	The primary quantitative outcome will be analysed by independent t-test of intervention against control arms, using monthly carbapenem prescribing data from June 2022 to April 2023. Secondary quantitative outcomes (a) and (b) will use the same method as the primary outcome. Tertiary outcomes will use the same method as the primary outcome or the Mann-Whitney U Test dependent upon the distribution of the variable. All quantitative outcome variables will be analysed independently using aggregated hospital-level data and it will not be possible, nor any attempt made, to link prescribing and clinical outcome data at the individual patient level. Secondary quantitative outcome (c) will be analysed by descriptive and exploratory statistics.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

Sample Size and Power Calculations	Based on middle quintile carbapenem prescribing volumes at baseline (2021-2022 Q1), the study will have 80% power ($\alpha=0.05$) to detect a change of 20% in the primary outcome with 8 NHS Trusts per arm. Sites will be screened for participation to optimize study power, based on statistical variation.
Limitations	Hospital participation in the study may be limited by operational pressures including COVID- 19 recovery or resurgence. Prescriber adoption and usage of MicroGuide is entirely voluntary so implementation rates may vary between institutions. DSMs will be developed by the project team, in collaboration with each NHS Trust. Statistical analysis will need to adjust for secular trends.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

1 Background and Rationale

1.1 Background

Infection is a common medical condition typically managed by non-specialists and trainee doctors report a lack of knowledge and confidence with regard to antimicrobial prescribing. [1-3] Antimicrobial resistance (AMR) varies according to pathogen epidemiology, geographical location and clinical setting, adding to prescribing complexity, with antimicrobial overuse and misuse commonplace, potentially exacerbating the problem of AMR.[4-6]

Clinical guidelines are a commonly-used antimicrobial stewardship intervention to facilitate safe and effective antimicrobial prescribing by non-specialists, with adherence to guidelines associated with reduced antimicrobial prescribing and lower mortality.[7-10] Conversely, prescribing *off-guideline* is associated with prescribing of broader spectrum antibiotics but not necessarily with better targeting of the likely pathogens.[11, 12] However, doctors report problems with guidelines, including version control and lack of accessibility in the work environment. Surveys of doctors reveal a demand for improved accessibility of guidelines, including via smartphones. [13-16] Emerging evidence demonstrates that providing antimicrobial prescribing guidelines and policies through the medium of a mobile device application can improve guideline adherence and policy compliance [17, 18] enhancing physician knowledge and impacting antimicrobial prescribing behaviour.[19, 20]

MicroGuide™ is a software application (app) for mobile electronic devices and web browser, providing a platform for locally-adaptable antimicrobial treatment guidelines and infection management advice for common infections, developed in response from feedback from trainee doctors. MicroGuide was co-designed and developed in 2011-12 by Horizon Strategic Partners (HSP) Ltd (now part of Induction Healthcare Group plc) and University Hospital Southampton NHS Foundation Trust in the United Kingdom (UK) and, from 2013, the app was licensed to other healthcare organisations in the UK and internationally.[21, 22] MicroGuide is currently licensed to 147 healthcare providers in primary and secondary care in 18 countries, including 91 of the 152 acute hospital Trusts in the National Health Service (NHS) in England and 5 healthcare organisations in the United States.[23] Each hospital has editorial independence to modify the app content to reflect local antimicrobial prescribing guidelines and to customise the app navigation architecture according to the preferences of local clinicians.[24] To date, the app has been downloaded free-of-charge over 250,000 times by users in 173 countries worldwide.

The basic MicroGuide app offers prescribers easy access to antimicrobial guidelines for quick reference, but it does not offer structured decision support based on specific patient details. MicroGuide has the ability to create decision support modules (DSMs) for particular conditions, so that prescribers can answer a series of conditional questions about factors such as disease severity, allergies, resistance risks and pregnancy status to be guided to a recommended choice of drugs or in some cases to seek further microbiology specialist

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

advice.

1.2 Rationale

Clinical decision support (CDS) does not automatically improve practice. CDS is often ignored, over-ridden or has unintended consequences. However, well-designed and well-implemented CDS can be welcomed by clinicians and demonstrate improved guideline adherence. Four systematic reviews (including two meta-analyses) of the impact of CDS on antimicrobial prescribing have been published within the last four years.[25-28] Most of the identified studies are non-randomized and of low methodological quality and considerable heterogeneity in CDS systems was reported. CDS was associated with an increase in appropriate selection of effective (active *in vitro* against isolated pathogenic microorganism) antimicrobial therapy, a reduction in mortality, decreased length of hospital stay, a reduction in treatment course length and reduced overall antimicrobial consumption.

Some physicians are dubious about the value of CDS for antimicrobial prescribing and so far there is limited evidence to show significant impact upon usage of broad-spectrum antimicrobial drugs or associated clinical outcomes. The purpose of this study is to definitively answer the question whether CDS delivered through the widely-adopted MicroGuide™ application can be shown to improve the clinical effectiveness and appropriateness of antimicrobial prescribing.

Clinical risk management

It is a legal requirement under the Health and Social Care Act 2012 for all clinical decision support software products used in the NHS in England to comply with the NHS Digital standards for clinical risk management, known as DCB 0129 and DCB 0160 (<https://digital.nhs.uk/services/clinical-safety/clinical-risk-management-standards>). This requirement is now aligned with the European regulations covering software as a medical device.

DCB 0129 places responsibilities upon CDS software manufacturers and DCB 0160 places responsibilities upon implementers of CDS software. The study team will work with each participating NHS Trust in the intervention arm to develop DCB0129 and DCB 0160 documentation.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

2 Objectives and Hypotheses

The intervention arm comprises NHS Trusts that implement MicroGuide DSMs for five common infections: community-acquired pneumonia; hospital-acquired pneumonia; urinary tract infection; skin and skin structure infection; intra-abdominal infection. The control arm comprises NHS Trusts using the standard 'browse' version of MicroGuide.

2.1 Primary Objective(s) & Hypothesis(es)

(O1) To determine whether there are statistically significant and clinically significant changes in patterns of carbapenem prescribing (data aggregated at hospital level) caused by implementation of decision support modules (DSMs) for common infections within the MicroGuide™ application.

(H1) The intervention arm will show lower levels of carbapenem prescribing than the control arm over a twelve-month period.

2.2 Secondary Objective(s) & Hypothesis(es)

(O2) To determine whether there are statistically significant and clinically significant changes in patterns of piperacillin-tazobactam prescribing caused by implementation of MicroGuide DSMs for common infections.

(O3) To determine whether there are statistically significant and clinically significant changes in antimicrobial resistance rates (*E. coli* resistance to piperacillin-tazobactam) caused by implementation of MicroGuide DSMs for common infections.

(O4) To analyse the opinions of MicroGuide DSM users about the effectiveness and usability of the modules and how they affect their prescribing practice.

(O5) To determine how quickly the MicroGuide DSMs are adopted in the intervention arm, whether usage is sustained over the study period and whether there is variation in patterns of usage by site or condition.

(H2) The intervention arm will show lower levels of piperacillin-tazobactam prescribing than the control arm over a twelve-month period.

(H3) The intervention arm will show lower levels of antimicrobial resistance rates (*E. coli* resistance to piperacillin-tazobactam) than the control arm over a twelve-month period.

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
<u>RevOps ID NO: NIS008543</u>	<u>CORE DRC Approval Date: 06-MAY-2022</u>

2.3 Exploratory Objective(s) & Hypothesis(es)

(O6) To determine for adult inpatients with a coded diagnosis matching any of the five MicroGuide DSMs whether adoption of the DSMs significantly affects clinical outcomes: length-of-stay, 30-day readmission, ICU admission and in-hospital mortality. **Note:** Data will be aggregated for the study population and it is neither planned nor possible to link clinical outcome to antimicrobial prescribing.

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
RevOps ID NO: NIS008543	<u>CORE DRC Approval Date:</u> 06-MAY-2022

3 Methodology

3.1 Summary of Study Design

The study is a two-arm parallel randomized controlled trial (RCT).

The setting is acute NHS Trusts in England that already use MicroGuide, targeting the middle band of carbapenem prescribing volume (defined below), measured as Defined Daily Doses (DDDs) per thousand admissions.

The recruitment period will be from February to June 2022. The quantitative study period will be from June 2022 to April 2023.

The primary outcome data collection will comprise monthly data releases from RxInfo (<https://www.rx-info.co.uk/products/define/>) and quarterly public data releases from Public Health England (PHE). Prescribing data is aggregated at hospital level and individual patient prescribing data is not available or required.

The tertiary quantitative outcome data collection will comprise a 12-month extract from NHS Digital based on the defined list of coded diagnoses. Clinical outcome data will be aggregated by NHS Trust for the cohort of patients with a coded diagnosis of one or more of five common infections (community-acquired pneumonia; hospital-acquired pneumonia; urinary tract infection; skin and skin structure infection; intra-abdominal infection). **Note:** The NHS Digital data set does not and cannot contain individual patient outcome data or treatment assignment details. Individual diagnoses or antimicrobial class(es) will not be identified in the data set.

Qualitative data will be collected from interviews conducted between September 2022 and April 2023.

Note: References to PHE and NHS Digital in this document should be understood to include whatever successor body assumes its duties for publishing antimicrobial prescribing data.

3.2 Study Population

NHS Trusts that already use MicroGuide.

Due to the wide variation in the primary outcome variable between NHS Trusts, the study will primarily seek to recruit from a middle band of prescribing so as to limit variance and increase the power of the study to detect significant change. This will be achieved by screening sites that offer to participate.

NHS Trust is the unit of analysis as the primary outcome data is only available at organizational unit level.

Each arm of the RCT will have the same number of NHS Trusts. The aim is to have 12 NHS Trusts per arm, but the minimum viable number is 8 per arm. There are currently 107 NHS Trusts in England that use MicroGuide. There are 21 NHS Trusts in the middle quintile of carbapenem prescribing volume among sites that use MicroGuide.

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
RevOps ID NO: NIS008543	<u>CORE DRC Approval Date: 06-MAY-2022</u>

All NHS Trusts that use MicroGuide will be invited to express interest to participate in the RCT. After screening, participating sites will be randomized to intervention or control arms.

Recruiting primarily from a middle band of carbapenem prescribing potentially represents a threat to the generalisability of the study findings but it is anticipated that any beneficial impact of the DSMs to acute NHS Trusts in the middle band will be amplified in those Trusts in the higher quintiles. This research will be reported transparently to emphasise the limitation that primary outcome findings may not be generalisable to acute NHS Trusts that are already in the lower quintiles of carbapenem prescribing.

Clinical outcome data from NHS Digital for all adult patients admitted to hospitals in both intervention and control arms during a period of 12 months and treated for any of the five common infections will be included.

3.3 Inclusion Criteria

Participant organisations will be recruited to the study from the following population (meeting all criteria):

- Acute NHS Trusts in England (to allow data extraction from PHE Fingertips website).
- Already using the MicroGuide application for at least 12 months (to allow for capture of baseline data and adjust for seasonality).
- Demonstrating carbapenem class antimicrobial consumption within the middle band for NHS Trusts in England to optimize study power.
- Making antimicrobial treatment guidelines available on their hospital intranet (as an alternative to MicroGuide) for the five common infections defined above.
- Willing to replace existing guidance for the five common infections (in browse format) within the MicroGuide application with decision-support modules.
- Willing to allow organizationally identifiable data extraction from RxInfo for monthly carbapenem prescribing volumes.

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

3.4 Exclusion Criteria

Healthcare organisations not meeting the inclusion criteria or declining to participate will be excluded.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

4 Variables and Epidemiological Measurements

4.1 Outcomes

Primary outcome: Carbapenem prescribing volume has been selected as the primary outcome variable because it is widely accepted as a key indicator for antimicrobial stewardship and the aggregated data are readily available from PHE (quarterly, public data) and RxInfo (monthly, data available to all NHS Trusts) to support power calculations and trial analysis. The prescribing volume is expressed as World Health Organisation DDDs per thousand admissions as a standardized reporting unit.

Secondary outcomes:

- a. Piperacillin-tazobactam prescribing volume measured as DDD per thousand admissions per NHS Trust.
- b. Antimicrobial resistance rates (*E. coli* resistance to piperacillin-tazobactam).
- c. MicroGuide software usage levels and patterns of use. This is solely an exploratory analysis.

Tertiary outcomes:

Length-of-stay, 30-day readmission, ICU admission and in-hospital mortality for adult inpatients with coded diagnosis of any of the five common infections covered by the decision support modules.

Qualitative outcomes: Opinions of decision support module users at participating hospitals (interviews).

Any herein described health outcomes, collected per the protocol, will be summarized as part of any interim analysis (if required) and in the final study report in addition to being reported in real-time as individual AE/s if the criteria in section 7 are met. Refer to section 7 for AE reporting requirements and procedures.

4.2 Covariates

Diagnosis definitions

The common infections covered by the DSMs and used to extract clinical outcome data are defined by ICD-10 codes (see <http://www.icd10data.com/ICD10CM/DRG>):

- a. bacterial pneumonia (ICD-10-CM J13, J14, J15, J18) (ICD-10 codes do not differentiate between community-acquired and hospital-acquired pneumonia.)
- b. infections of the kidney & urinary tract (ICD-10-CM MS-DRG v34.0 Group 689 and Group 690)
- c. infections of the skin and subcutaneous tissue (ICD-10-CM L00 to L08)
- d. major gastrointestinal disorders and peritoneal infections (ICD-10-CM MS-DRG v34.0 Groups 371, 372 and 373).

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
<u>RevOps ID NO: NIS008543</u>	<u>CORE DRC Approval Date: 06-MAY-2022</u>

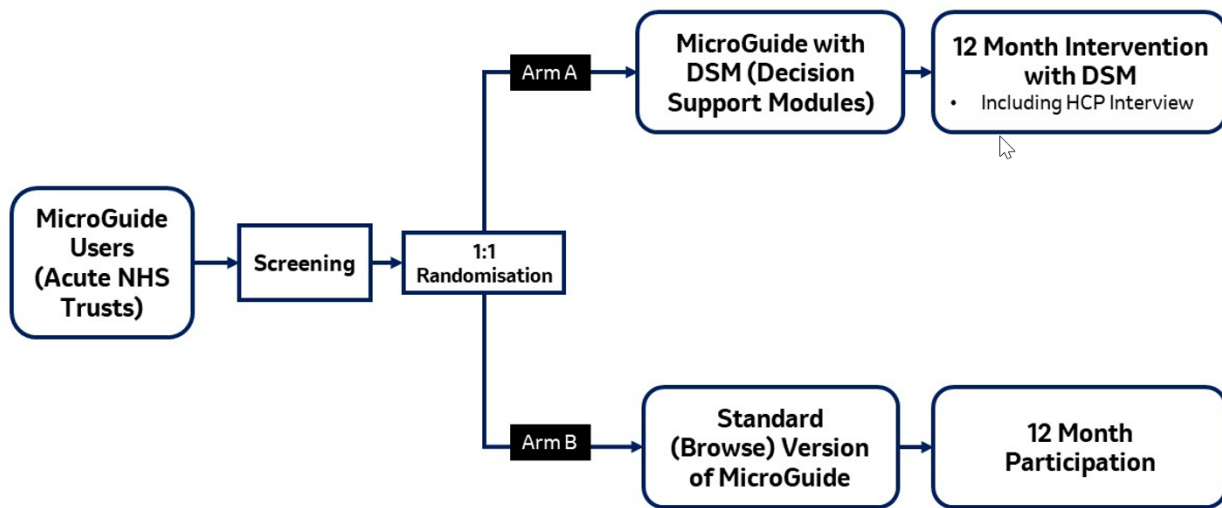
4.3 Exposure

Primary exposure is deployment of the decision-support module (DSM) functionality within the MicroGuide app for five common infections for the 12-month period following Trust implementation of the MicroGuide DSMs. A full year is stipulated as a minimum requirement to guarantee robust analysis of a time series incorporating seasonal variations.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

5 Study Flow Chart

Figure 1 Trial Design Overview



Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

6 Study Procedures

6.1 Study Procedures

The Study Diagram in Section 5 summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety.

6.1.1 Administrative Procedures

6.1.1.1 Protection of Human Subjects

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

This is a database study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol. Individual patient consent will not be required because the study will collect and analyse aggregated outcome data and does not require individual chart review.

The lead clinician responsible for implementation of the app at each eligible organisation will be invited by Horizon Strategic Partners (MicroGuide software developers) to participate and, if they give consent, their contact details will then be forwarded to the research team to formally recruit them to the study. It is anticipated that the majority will be specialist antibiotic pharmacists, consultant medical microbiologists or

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

infectious diseases physicians. The study will also be promoted through the Clinical Research Network operated by the National Institute for Health Research (NIHR). Other informal recruitment and advertisement methods will be used, such as sharing information on social media, with antimicrobial and research networks and in conference presentations and personal conversations. Reminders may be sent to Trusts to encourage participation. The lead clinicians will be required to obtain organization-level consent for study participation, specifically to be randomized to mandatory implementation of decision support modules within the MicroGuide app or to continue using the standard version of the MicroGuide application (i.e. browse format) for the five common infections. It is anticipated that organization level consent will require approval by an internal governance committee such as the hospital Antimicrobial Stewardship Committee or Drug & Therapeutics Committee or equivalent. The lead clinicians will be asked to consent to analysis of app use statistics and aggregated Trust-level antibiotic prescribing (from the RxInfo Define software), resistance (from Public Health England Fingertips website) and clinical outcome data (from NHS Digital).

6.1.1.1 Quantitative data

Quantitative data will be provided by RxInfo, Public Health England (PHE) and NHS Digital from datasets of Trust-level antibiotic prescribing, antibiotic resistance and clinical outcomes respectively. No patient identifier data will be required for this study. The identity of participating hospital Trusts will also be concealed by the researcher and will not be available to Horizon Strategic Partners or the study sponsor.

6.1.1.2 Qualitative data

Sampling

A purposive sample of up to 30 health professionals, comprising junior and senior doctors and nurse prescribers using the MicroGuide decision support modules for a minimum of 6 months, will be selected from the intervention group acute hospital Trusts. [29, 30] The sample will be selected across intervention Trust sites so that the range of infections and adult in-patient medical specialities where MicroGuide is used will be represented.

Recruitment and consent

Staff members that have registered with Horizon Strategic Partners and have downloaded and are actively using the MicroGuide app at participating intervention hospitals will be contacted by e-mail by Horizon Strategic Partners to offer them the opportunity of participating in the interview phase of the study. The e-mail communication will include a copy of the Participant Information Sheet and details of how to contact the research team, independently of Horizon Strategic Partners. Interested individuals will contact a member of the research team, and will be sent further information about the study, including a consent form, and will

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

have an opportunity to ask questions about the study. Written consent will be obtained from all interviewees prior to data collection. Consent will be re-affirmed verbally at the commencement of the interview. Interviews will take place at a time convenient to participants during their personal time and they will be offered compensation with an Amazon voucher.

Qualitative data from surveys and interviews with decision-support module users will be anonymised by the researcher and the identity of survey respondents and interviewees will not be available to Horizon Strategic Partners or the study sponsor.

Data collection

Participants will be invited to take part in a semi-structured interview, expected to last for up to 45-minutes. One- to-one interviews, instead of focus groups, will be used due to the potentially sensitive nature of the questions around personal antimicrobial prescribing habits. Interviews will be conducted on the telephone or face-to-face, with an experienced interviewer and will be digitally audio-recorded. The interviews will explore: (i) adoption of the decision-support element of the app in practice (ii) when and why clinicians use/don't use the decision- support function of the app; (iii) evolution of use of DSMs over time and how clinicians currently use the DSMs; (iv) opinions on usability, content and usefulness of the app's decision-support modules (v) views on the effectiveness of the DSMs, including influence of the DSMs on individual prescribing behaviour and implications for patient safety; (vi) opinions of how the DSMs could be improved; and (vii) barriers/enablers to DSM use. Interviews will continue until saturation of emerging themes is achieved.

Interview data will be analysed using a thematic analysis process.[31] Interview data will be transcribed by University-approved independent transcription services, who will store and manage data in accordance with our ethical approval and University regulations. This will include anonymising any identifiable data in audio-recordings during transcription. Thematic analysis of data will take place at the researcher's place of employment and Portsmouth Hospitals University NHS Trust. Anonymised data will be shared with the Universities of Southampton and Portsmouth for the process of data analysis. Transcripts will be transferred via encrypted secure software. NVivo qualitative data management software will be used to help manage the data.

The interview guide was developed drawing on published evidence of: influences on hospital antimicrobial prescribing behaviour, the impact of clinical decision-support apps on health professional decision- making and findings from our previous research into the impact of the MicroGuide app (manuscript under consideration). The interview guide also incorporate the elements of the COM-B model (Capability, Opportunity, Motivation - Behaviour), which is a psychological theory-informed framework that characterizes and explains the cognitive mechanisms that might lead individuals to modify their behavior. [32, 33]

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
<u>RevOps ID NO: NIS008543</u>	<u>CORE DRC Approval Date: 06-MAY-2022</u>

6.1.1.3 App Patterns of Use

Written consent will be sought for the release of app usage statistics (held by Horizon Strategic Partners) from the healthcare professional with responsibility for implementing the MicroGuide App at NHS hospitals licensing the software. Personal information of individual app users (usually healthcare professionals) will not be required for this phase of the study.

Horizon Strategic Partners (MicroGuide app software developer) has agreed to provide (free-of-charge) routinely- collected system access statistics for all consenting NHS Trusts currently licensing the app within the target population for analysis (n=24), in order to determine patterns of app use by establishing which groups of healthcare practitioners are using the app, when and how often, and for which infections is guidance most frequently accessed

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

7 Safety and Product Quality Complaint Reporting and Related Procedures

Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

Introduction

This is a primary data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol.

7.1 Adverse Event and Product Quality Complaint Reporting

7.1.1 INVESTIGATOR RESPONSIBILITY:

Primary Data Collection (telephone/face to face interviews): If adverse events (AEs) or product quality complaints (PQCs) are identified following use of any Sponsor product, then the AE* and/or PQC must be reported according to Table 1. If any health outcomes are described in section 4.1, they must be assessed for AE reportability according to Table 1 (refer to section 4.1 for more information).

*For the purposes of this protocol, the term “AE” collectively refers to the following reportable events (refer to section 7.2 for definitions):

- Serious adverse events (SAEs), including death due to any cause
- Non-serious adverse reactions (NSARs)
- Special situations

AEs, PQCs, and AEs that occur in combination with PQCs, or spontaneously reported events, should all be captured using the AE/PQC report form for each patient and reported according to Table 1.

The investigator must evaluate each SAE for causality and record causality on the report form for each SAE and NSAR reported.

Secondary data review (structured, quantitative data from PHE and RxInfo which are aggregated at the hospital Trust level): No reporting of individual adverse events or product quality complaints to regulatory agencies is planned for this database review because there is no access to individual patient/subject records and it is not possible to assess the causality of individual cases. Any health outcomes (if collected per section

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

4.1), including any that qualify as adverse events, will be summarized as part of any interim analysis (including safety analysis, if required) and in the final study report, which will be provided to regulatory agencies by the Sponsor as required.

If an investigator elects to spontaneously report any suspected adverse reactions or product quality complaints, they should be reported per Table 1.

Table 1: AE and PQC Reporting Timeframes and Process for Investigators

AEs AND PQCs	INVESTIGATOR TIMEFRAMES Investigator to Sponsor [1]
SAE regardless of causality Serious Special Situation, regardless of causality	24 hours from receipt
NSAR Non-serious Special Situation, regardless of causality	10 CD from receipt
PQC with or without an AE (SAE/NSAR/Special situation)	24 hours from receipt
Follow-up to any AE-submit using above timeframes	
BD-Business Day; CD-Calendar Day	
Non-Sponsor Products: If the investigator elects to submit AEs/PQCs for non-Sponsor products , they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.	
[1] Investigator to Sponsor: AEs and PQCs for Sponsor products are submitted to Sponsor for reporting to worldwide regulatory agencies as appropriate	
Submitting AEs and PQCs to MSD Global Safety: All AEs and PQCs must be submitted to MSD UK Pharmacovigilance Department FAX [00 32 2402 5990] or submitted directly to pv.uk@msd.com via password protected email, in English using the AE/PQC reporting form.	

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
<u>RevOps ID NO: NIS008543</u>	<u>CORE DRC Approval Date: 06-MAY-2022</u>

7.2 DEFINITIONS

7.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

7.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

7.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

7.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 7.2.3.

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
<u>RevOps ID NO: NIS008543</u>	<u>CORE DRC Approval Date: 06-MAY-2022</u>

7.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent
- Unexpected Therapeutic Benefit/Effect

7.2.6 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

7.2.7 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

7.2.8 Sponsor's product

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
<u>RevOps ID NO: NIS008543</u>	<u>CORE DRC Approval Date: 06-MAY-2022</u>

7.2.9 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

Primary Data Collection

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

8 Statistical Analysis Plan

8.1 Statistical Methods

Statistical significance

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level. All differences between study arms will be presented with 95% confidence intervals.

Categorical and Continuous data

Categorical outcomes are summarised by numbers and percentages. Continuous outcomes data are summarised by mean and standard deviation (SD) if data are normally distributed or median and interquartile range (IQR) if data are skewed. Any difference between the study arms will be computed using the appropriate statistical parametric/non-parametric test and reported using tables and graphs.

The statistical analysis will be performed using SAS version 9.4, SAS Institute Inc., Cary, NC, USA.

8.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest

Carbapenem prescribing volume measured as Defined Daily Doses (DDD) per thousand admissions per NHS Trust will be analysed and compared between study arms using a parametric test - Two Independent Samples T- Test. Mean, standard deviation, ranges and 95% confidence intervals (CIs) will be reported by arm and for the difference between arms.

We also plan to perform time series analysis of the primary outcome between the two arms, but trend data are not publicly available for all NHS Trusts so we cannot make a power calculation based on this approach. When Trusts sign up to participate in the study, we will ask for consent to access their previous twelve months' data (via RxInfo) and the monthly data during the study period.

8.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest

Piperacillin-tazobactam prescribing volume measured as DDD per thousand admissions per NHS Trust and antimicrobial resistance rates measured as average proportion of piperacillin-tazobactam resistant *E. coli* blood specimens will be analysed and compared between study arms using a parametric test - Two Independent Samples T-Test. Mean, SD, ranges and 95% CI will be reported by arm and for the difference between arms.

8.1.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest

Clinical outcomes: length-of-stay, 30-day readmission, ICU admission and in-hospital mortality aggregated

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

for a cohort of adult inpatients with coded diagnosis of any of the five common infections covered by the decision support modules will be analysed and compared between the study arm using parametric/non-parametric tests such as Two Independent Samples T-Test/Mann-Whitney U Test dependent upon the distribution of the clinical outcome variable. It will not be possible to analyse clinical outcome by diagnosis or by selection of antimicrobial at the individual patient level. All prescribing and clinical outcome data will be aggregated at hospital level.

8.2 Bias

8.2.1 Methods to Minimize Bias

The source data for the primary and secondary outcomes is extracted from operational hospital pharmacy systems and patient administration systems and is used for national reporting by PHE.

The primary outcome data is total inpatient carbapenem volume per NHS Trust, including both adults and children. As it is not possible to differentiate between adult and paediatric carbapenem prescribing, the study will record the number of paediatric beds per NHS Trust to ensure that the results are not skewed. Paediatric prescribing of carbapenems is typically a fairly small percentage of the Trust total, so this is not anticipated to pose a significant problem.

8.2.2 Limitations

Hospital participation in the study may be limited by operational pressures including COVID-19 recovery or resurgence. Prescriber adoption and usage of MicroGuide is entirely voluntary so implementation rates may vary between institutions and app use metrics will be used to perform a sensitivity analysis for fidelity to the intervention. Each participating NHS Trust in the intervention arm will work with the study team to develop and test DSMs based upon treatment guidelines from the National Institute for Health and Care Excellence (NICE), and local hospital policies. Statistical analysis will need to adjust for secular trends. The yearly trend is studied and accounted in the sample size from the design.

We will obtain 2018 and 2019 primary outcome data as an extended baseline to assess COVID impact so far, using data on COVID admissions per Trust from 2019 onwards to explore any correlation with changes in the primary outcome that we are measuring.

Although the primary objective is changes in antibiotic prescription of a given class, these cannot and should not be linked to any of the measured outcomes in the secondary and tertiary objectives.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

8.3 Sample Size and Power Calculations

Based on middle band carbapenem prescribing volumes at baseline, the study will have 80% power ($\alpha=0.05$) to detect a change of 20% in the primary outcome with 8 NHS Trusts per arm.

Preliminary data from the MicroGuide-1 study, to evaluate the impact of the implementation of the browse version of the MicroGuide app in 34 UK hospitals, indicate that an increasing trend in carbapenem prescribing during the two years prior to introduction of MicroGuide was reversed to a statistically significant extent following implementation, resulting in a relative decrease in carbapenem prescribing per 1,000 patient admissions of 11.3% in the year after implementation, without any decision-support (manuscript in preparation).

The most recent systematic review and meta-analysis by Laka and colleagues [27] reported findings from 9 studies of hospital consumption in a hospital setting before and after implementation of computerised decision support systems (CDSS). A reduction in total antimicrobial consumption following CDSS implementation was reported by 8 of the 9 studies, ranging from a 2.6% reduction to a 66% reduction (median 12% reduction).

Therefore the 20% level of change is proposed as a pragmatic balance of what is clinically significant and what is practically feasible given the population characteristics and the desired statistical power.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

9. Administrative and Regulatory Details

9.1 Confidentiality

9.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

9.1.2 Confidentiality of Study Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), and if applicable Regulatory Agency representatives may consult and/or copy study documents to verify worksheet/case report form data. By signing this protocol, the investigator agrees to treat all study data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

9.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel (if applicable), may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. By signing this protocol, the investigator expressly consents to these uses and disclosures. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. The investigator is hereby notified that the collection, processing and sharing of their personal data with respect to adverse event reports to the Sponsor and regulatory agencies occurs on the basis of performance of a legal obligation, and the investigator expressly consents to these uses and disclosures when reporting such events to other investigators.

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
RevOps ID NO: NIS008543	<u>CORE DRC Approval Date: 06-MAY-2022</u>

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

9.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

9.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice (GPP) and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, and if applicable regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all study- relevant documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. Documentation applicable to this type of study may include, in addition to the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, the Sponsor will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or study report CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

9.4 Quality Management System

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP), and applicable laws and regulations. If a significant

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

9.5 Data Management

All data collected for the study should be recorded accurately, promptly, and legibly. The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

If this study has been outsourced, the institutional policies of the supplier should be followed for development of data management plans. However, the supplier should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

9.6 Institutional Review Board/ Independent Ethics Committees

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and if applicable such information will be divulged to the Institutional Review Board, Ethics Review Committee (IRB/IEC) or similar or expert committee, affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

The investigator also agrees to allow IRB/IEC review of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule correspondence with IRBs/IECs and consent forms.

If required by the site's IRB/IEC, in the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

10 Publications

Any publications related to the study will need to be reviewed/approved by the Sponsor prior to submitting results externally.

Two journal papers are planned: one focusing on the quantitative results and one concentrating on the qualitative findings. A summary of results will be made available to all participating NHS Trusts and a white paper will be posted on Horizon's web site. These forms of dissemination are planned for 2023-2024.

There may be additional dissemination at academic or industry conferences at earlier stages of the study to present preliminary findings.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

11. References

1. Beovic B, Dousak M, Pulcini C, et al. Young doctors' perspectives on antibiotic use and resistance: a multinational and inter-specialty cross-sectional European Society of Clinical Microbiology and Infectious Diseases (ESCMID) survey. *J Antimicrob Chemother* **2019**; 74(12): 3611-8.
2. Gharbi M, Moore LS, Castro-Sanchez E, et al. A needs assessment study for optimising prescribing practice in secondary care junior doctors: the Antibiotic Prescribing Education among Doctors (APED). *BMC Infect Dis* **2016**; 16(1): 456.
3. Kajamaa A, Mattick K, Parker H, Hilli A, Rees C. Trainee doctors' experiences of common problems in the antibiotic prescribing process: an activity theory analysis of narrative data from UK hospitals. *BMJ Open* **2019**; 9(6): e028733.
4. Cusini A, Rampini SK, Bansal V, et al. Different patterns of inappropriate antimicrobial use in surgical and medical units at a tertiary care hospital in Switzerland: a prevalence survey. *PLoS One* **2010**; 5(11): e14011.
5. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. *Arch Intern Med* **2003**; 163(8): 972-8.
6. Pulcini C, Cua E, Lieutier F, Landraud L, Dellamonica P, Roger PM. Antibiotic misuse: a prospective clinical audit in a French university hospital. *Eur J Clin Microbiol Infect Dis* **2007**; 26(4): 277-80.
7. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* **2017**; 2: CD003543.
8. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic Review and Meta-analysis of Clinical and Economic Outcomes from the Implementation of Hospital-Based Antimicrobial Stewardship Programs. *Antimicrob Agents Chemother* **2016**; 60(8): 4840-52.
9. Martinez R, Reyes S, Lorenzo MJ, Menendez R. Impact of guidelines on outcome: the evidence. *Semin Respir Crit Care Med* **2009**; 30(2): 172-8.
10. Schuts EC, Hulscher ME, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. *Lancet Infect Dis* **2016**; 16(7): 847-56.
11. Mol PG, Denig P, Gans RO, et al. Limited effect of patient and disease characteristics on compliance with hospital antimicrobial guidelines. *Eur J Clin Pharmacol* **2006**; 62(4): 297-305.
12. Van der Velden LB, Tromp M, Bleeker-Rovers CP, et al. Non-adherence to antimicrobial treatment guidelines results in more broad-spectrum but not more appropriate therapy. *Eur J Clin Microbiol Infect Dis* **2012**; 31(7): 1561-8.
13. Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* **2004**; 8(6): iii-72.
14. Markley JD, Pakyz A, Bernard S, et al. A survey to optimize the design of an antimicrobial stewardship smartphone app at an academic medical center. *Am J Infect Control* **2017**; 45(3): 317-20.
15. May L, Gudger G, Armstrong P, et al. Multisite exploration of clinical decision making for antibiotic use by emergency medicine providers using quantitative and qualitative methods. *Infect Control Hosp Epidemiol* **2014**; 35(9): 1114-25.
16. Moodley A, Mangino JE, Goff DA. Review of infectious diseases applications for iPhone/iPad and Android: from pocket to patient. *Clin Infect Dis* **2013**; 57(8): 1145-54.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

17. Charani E, Gharbi M, Moore LSP, et al. Effect of adding a mobile health intervention to a multimodal antimicrobial stewardship programme across three teaching hospitals: an interrupted time series study. *J Antimicrob Chemother* **2017**; 72(6): 1825-31.
18. Yoon CH, Ritchie SR, Duffy EJ, et al. Impact of a smartphone app on prescriber adherence to antibiotic guidelines in adult patients with community acquired pneumonia or urinary tract infections. *PLoS One* **2019**; 14(1): e0211157.
19. Bochicchio GV, Smit PA, Moore R, et al. Pilot study of a web-based antibiotic decision management guide. *J Am Coll Surg* **2006**; 202(3): 459-67.
20. Tuon FF, Gasparetto J, Wollmann LC, Moraes TP. Mobile health application to assist doctors in antibiotic prescription - an approach for antibiotic stewardship. *Braz J Infect Dis* **2017**; 21(6): 660-4.
21. Jahn HK, Jahn IH, Roland D, Lyttle MD, Behringer W, Peruki. Mobile device and app use in paediatric emergency care: a survey of departmental practice in the UK and Ireland. *Arch Dis Child* **2019**; 104(12): 1203-7.
22. Llewelyn MJ, Hand K, Hopkins S, Walker AS. Antibiotic policies in acute English NHS trusts: implementation of 'Start Smart-Then Focus' and relationship with *Clostridium difficile* infection rates. *J Antimicrob Chemother* **2015**; 70(4): 1230-5.
23. Horizon_Strategic_Partners. MicroGuide app customer data. In: Hand K: Personal Communication, **05 June 2020**.
24. Hoff BM, Ford DC, Ince D, et al. Implementation of a Mobile Clinical Decision Support Application to Augment Local Antimicrobial Stewardship. *J Pathol Inform* **2018**; 9: 10.
25. Carracedo-Martinez E, Gonzalez-Gonzalez C, Teixeira-Rodrigues A, et al. Computerized Clinical Decision Support Systems and Antibiotic Prescribing: A Systematic Review and Meta-analysis. *Clin Ther* **2019**; 41(3): 552-81.
26. Curtis CE, Al Bahar F, Marriott JF. The effectiveness of computerised decision support on antibiotic use in hospitals: A systematic review. *PLoS One* **2017**; 12(8): e0183062.
27. Laka M, Milazzo A, Merlin T. Can evidence-based decision support tools transform antibiotic management? A systematic review and meta-analyses. *J Antimicrob Chemother* **2020**; 75(5): 1099-111.
28. Rittmann B, Stevens MP. Clinical Decision Support Systems and Their Role in Antibiotic Stewardship: a Systematic Review. *Curr Infect Dis Rep* **2019**; 21(8): 29.
29. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field Methods* **2006**; 18(1): 59-82.
30. Hennink MM, Kaiser BN, Marconi VC. Code Saturation Versus Meaning Saturation: How Many Interviews Are Enough? *Qual Health Res* **2016**.
31. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* **2006**; 3(2): 77-101.
32. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implement Sci* **2012**; 7: 37.

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
<u>RevOps ID NO: NIS008543</u>	<u>CORE DRC Approval Date: 06-MAY-2022</u>

33. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* **2011**; 6: 42.

Product: MK-7625A	Protocol/Amendment Version No.: 3.0
RevOps ID NO: NIS008543	CORE DRC Approval Date: 06-MAY-2022

12 SIGNATURES

12.1 Sponsor's Representative

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
<u>RevOps ID NO: NIS008543</u>	<u>CORE DRC Approval Date: 06-MAY-2022</u>

12.2 Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other project plans and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and the Use and Disclosure of Personal Data notice provided to me, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

Product: MK-7625A	<u>Protocol/Amendment Version No.: 3.0</u>
<u>RevOps ID NO: NIS008543</u>	<u>CORE DRC Approval Date: 06-MAY-2022</u>

12.3 Supplier

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and in order to perform any agreement between myself and the Sponsor, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	