FULL/LONG TITLE OF THE STUDY
AccessCMD: a 'next generation registry' in patients with Cardiometabolic Disease

SHORT STUDY TITLE / ACRONYM
AccessCMD

PROTOCOL VERSION NUMBER AND DATE
Version: 2.0
Date: 17 APRIL 2024

SPONSORS:	Cohort Science Ltd
FUNDERS:	Cohort Science Ltd

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in accordance with the current Good Clinical Practice (GCP) regulations and in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, 21 Code of Federal Regulations (CFR) Parts 11, 46, 50, and 56, the Sponsor's standard operating procedures (SOPs), and other regulatory requirements. Any changes in procedure will only be made if necessary to eliminate immediate hazards and/or to protect the safety, rights, or welfare of participants.

I agree to ensure that the confidential information contained in this document 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 findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

I agree to keep records on all subject information collected during the study in accordance with the current GCP, local and national regulations.

For and on behalf of the Study Sponsor:

Signature: Date:
..../...../.....

Name (please print):
.....

Position:
.....

Chief Investigator:

Signature: Date:
..../...../.....

Name: (please print):
.....

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
AccessCMD protocol	February 12, 2024	Draft version 0.1
AccessCMD protocol	February 28, 2024	Final reviewed version
AccessCMD protocol	April 17, 2024	Changes to wording around sub-studies to provide clarification on the different types.

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KEY REGISTRY CONTACTS

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Committees	AccessCMD management committee accesscmdcommittee@cohort.science AccessCMD executive committee: Principal Investigator: Dr Mark Toshner Cohort Science representative: Dr Anil Jina uMed Representative: Dr Matthew Wilson Primary Care representative (UK): Dr. Vijaykumar Elango Industry Representative – TBC

REGISTRY SUMMARY

Registry Title	AccessCMD: a 'next generation registry' in Cardiometabolic Disease
Internal ref. no. (or short title)	AccessCMD
Study Design	Research database Integrated clinical research platform Research registry Observational study
Study Participants	Patients with a diagnosis of Cardiometabolic Disease coded in health records.
Planned Size of Sample	No upper limit Target in year 1: 5000 participants
Follow-up duration	20 years
Planned Study Period	20 years
Research Question/Aim(s)	1. To build a registry of participants with a diagnosis of Cardiometabolic Disease to access new research opportunities. 2. To create a core clinical dataset including questionnaire data, genetic and other linked clinical data. 3. To improve equitable access to cardiometabolic disease research opportunities.

FUNDING AND SUPPORT IN KIND

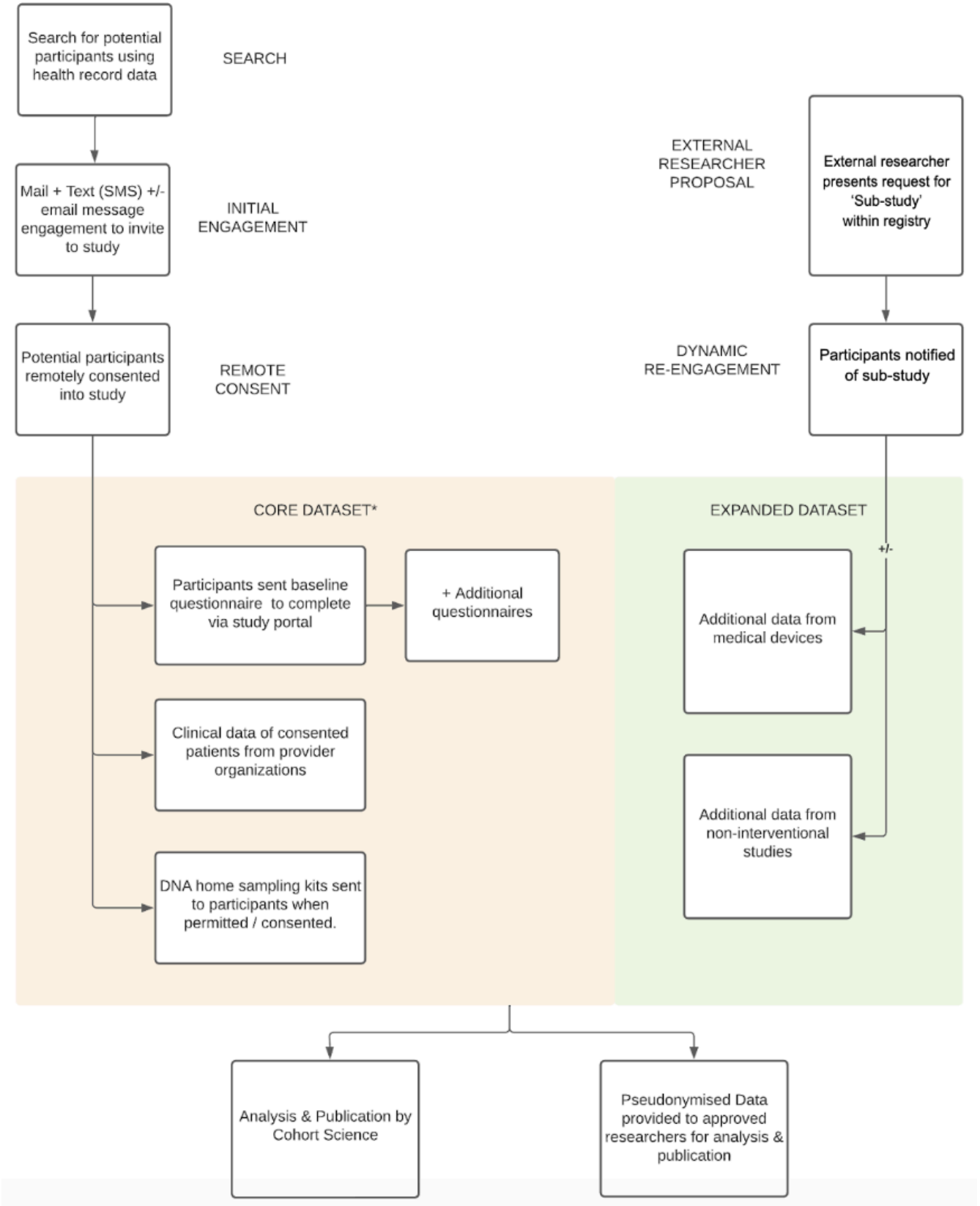
FUNDER(S)	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
Cohort Science Ltd 8 Warner Yard, London, EC1R 5EY Email: info@cohort.science Phone: +44 (0) 2033 030329	Sole funder of registry

Table 1. List of abbreviations and definitions of terms

Abbreviation	Definition
BMI	Body Mass Index
CCD	Core Clinical Data
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMD	Cardiometabolic Disease
COA(s)	Clinical Outcome Assessment(s)
CS	Cohort Science
DSA	Data Sharing Agreement
EHR	Electronic Health Record
FAQ	Frequently Asked Questions
GCP	Good Clinical Practice
HCI	Healthcare Institution
HCP	Healthcare Professional
ICF	Informed Consent Form
ICH	International Council on Harmonization
IRB	Institutional Review Board
MoCA	Montreal Cognitive Assessment
NHS	National Health Service
PCP	Primary Care Physician
PI	Principal Investigator
PPI	Patient Public Involvement
PROs	Patient Reported Outcomes
SMS	Short Messaging Service (i.e. text message)
SOP	Standard Operating Procedure

KEYWORDS
Cardiometabolic disease, registry, research database, tissue bank, observational studies, clinical trials, medical devices

REGISTRY FLOW CHART (Figure 1)



REGISTRY PROTOCOL

1 BACKGROUND

Complex cardiometabolic disease is responsible for the largest share of morbidity and mortality worldwide[1]. With the myriad of complications of cardiovascular multimorbidity the healthcare costs are steadily rising. The direct estimated healthcare cost burden of, for example, downstream heart failure alone in only the US is predicted to rise to $53 billion by the next decade[2]. There is an urgent and pressing need for population level solutions to address this rising pandemic. In the 'at risk' population, there are many identified evidence-based preventative and treatment solutions to avoid and mitigate the most severe adverse outcomes. In addition, there is a strong association between increased BMI and obesity with cardiometabolic multimorbidity, whereby the risk of cardiometabolic multimorbidity increases from double in overweight people, to four and more than ten times in people with mild and severe obesity respectively, compared to individuals with a healthy BMI. Literature highlights the need to acknowledge this association in clinical guidelines, and importantly the need to actively screen overweight and obese patients particularly for diabetes and vascular disease.[3]

2 RATIONALE

The main aim of this project is to develop a 'next generation registry' for participants with CMD and associated risk factors. The registry will be used to build a cohort of participants and collect a core clinical dataset. Participants can then be offered the potential to be involved in further research opportunities in the form of observational studies, medical device studies and clinical trials of investigational medicinal products.

3 FRAMEWORK

Cohort Science is the study sponsor for AccessCMD and has a Registry Participation Agreement in place with each participating healthcare institution (HCI). The Registry Participation Agreement does not require electronic medical record data held by a HCI to be shared directly with Cohort Science. In accordance with an individual's right under HIPAA to access their own health information, Cohort Science will simply facilitate submitting, on the patient's behalf, a signed patient access request to each HCI to release health information to support research.

AccessCMD utilizes the services and technology of uMed Technologies Inc. (uMed) to minimize cost and effort for HCI's to recruit study participants and maximize patient access to research. uMed will facilitate, as a business associate to the HCI, patient outreach services to obtain consents and authorizations to enable patient access to disclose patient data to the Sponsor and Sponsor's designees in compliance with the HIPAA Regulations and other applicable law. The services provided by uMed to a participating HCI are limited to facilitating patient outreach under the direction and on behalf of a designated researcher at the HCI to request research consent and authorization from eligible research participants. uMed does not identify or communicate independently with patients for research unless specifically requested to do so by a HCI. Therefore the data requested by uMed to facilitate outreach is limited to a roster of eligible patients and relevant contact information (data specification included). Once a patient has consented, uMed will be responsible for ongoing patient engagement and collection of eCOAs and ePROs.

[1] https://pubmed.ncbi.nlm.nih.gov/30496104/
[2] https://pubmed.ncbi.nlm.nih.gov/23616602/
[3] https://pubmed.ncbi.nlm.nih.gov/28626830/

Both uMed (a Delaware Corporation) and Cohort Science (a UK Limited Company) are subsidiaries of the UK parent company Umedeor Ltd.

The intent of AccessCMD is to create a 'next generation registry' that collects a core clinical set of data from consented patients (AccessPD Core Clinical Data [CCD]), consisting of clinical data from their electronic health records (EHR) and relevant Patient Reported Outcomes (PROs) and other information obtained via questionnaires. It will also bring research opportunities to patients with which they can participate. Decisions regarding the ongoing conduct of the study, inclusion of new research opportunities ('sub-studies'), data and participant access requests, manuscript writing and dissemination of results will be taken by the AccessCMD management committee. A summary of the workflow and process for AccessCMD can be found in **Appendix 1.**

Academic and commercial research teams may also submit proposals for 'sub-studies' to the AccessCMD management committee. A sub-study is defined as a project that is undertaken with a researcher external to Cohort Science. Decisions regarding the conduct of these sub-studies will be made by the AccessCMD management committee. Further details of the governance model for different types of sub-studies can be found in **Appendix 2**.

Any clinical trials or other interventional studies using participants identified through AccessCMD will be conducted as standalone trials with separate protocols and independent IRB review and approval prior to commencement.

4 ROLES AND RESPONSIBILITIES

4.1 Registry Management Committee:

- Chief Investigator: Mark Toshner MD FRCP
- Anil Jina, MD (Secretary, Cohort Science)
- Matthew Wilson, MB BS (CEO, uMed)

4.2 Patient and Public Involvement (PPI) Group

AccessCMD will undertake regular PPI group consultations to capture broader feedback on the activity taking place within the registry. Previous PPI groups have been organized in the UK and the intention is to build collaborations with CMD patient advocacy groups in the UK, US and Canada.

5 PROTOCOL CONTRIBUTORS

- Chief Investigator: Mark Toshner, MD FRCP
- Cohort Science Ltd: Anil S Jina, MD

Cohort Science Ltd has input on the registry design and conduct; data analysis and interpretation; manuscript writing and dissemination of results.

After initial setup, the AccessCMD Management Committee will control the final decisions about the conduct of the registry, the inclusion of 'sub-studies', data analysis and interpretation, manuscript writing and dissemination of results.

6 RESEARCH AIM(S)

The principal **aim** of this project is to develop a new platform for research (described throughout as a 'next generation registry' and called AccessCMD), which will establish a core clinical dataset for CMD and associated risk factors to help streamline widespread, equitable access to additional research opportunities for patients with CMD.

6.1 Objectives

1) To establish a 'next generation registry' for CMD.
2) To provide information, obtain consent and recruit patients to AccessCMD.
3) To collect a core clinical set of data from consented patients (AccessCMD Core Clinical Data [CCD]), which would consist of clinical data from their EHR and relevant PROs and other information obtained via questionnaires.
4) To collaborate with other entities in the form of 'sub-studies' and offer these new opportunities to participants who are registered with AccessCMD. Sub-studies may require protocol amendments and/or additional IRB approval.

6.2 Outcomes

The main outcome of this project is to build an engaged and active group of participants in AccessCMD, contributing to the AccessCMD CCD, who are also exposed to a range of additional research opportunities, which will streamline progress in CMD research and drive better outcomes for patients.

7 REGISTRY DESIGN

Potential participants will be identified by designated HCP(s) at a contracted HCI from EHR according to the study inclusion and exclusion criteria outlined below (i.e. coded diagnosis of PD). The initial contact will be via short message service (SMS)/text and/or email sent by uMed on behalf of the patient's HCI (see figure 1), which will invite potential participants to join AccessCMD. Potential participants will receive a link in the SMS to view information about AccessCMD on their smartphone or computer browser. This information will include the aims of the registry and steps required to participate, which includes consent to enroll in the registry and providing HIPAA authorization (see Appendix 6). Potential participants may also receive a letter sent by uMed or an electronic communication sent by their HCI as a precursor to receiving SMS communications about AccessCMD.

AccessCMD will invite participants to complete ePROs and other medical questionnaires to generate a set of core clinical data for research (AccessCMD CCD). At the same time, their EHR records will also be linked to the registry. A list of Clinical Outcome Assessments (COAs) is provided below. Additional COAs which may be administered in the future will require protocol amendments and IRB approval.

Clinical Outcome Assessments (COAs)

All participants recruited will have the following information extracted from their EHR or answer questions to provide more details:

- Demographics (Age, sex, ethnic group, race, education (level/years))
- Comorbidities (e.g. sleep apnea, obesity, acid reflux)
- Vital signs (weight, height, blood pressure, heart rate, oxygen saturation)
- Routinely collected blood test results (such as liver, renal and thyroid functions, glucose, HbA1c, hematology tests, troponin and N-terminal pro B-type natriuretic peptide etc.)
- Current and previous medications
- Date of symptom onset and first symptom
- Specific diagnosis
- Date of diagnosis and setting (primary or secondary care)

- Name of specialist and/or treatment center
- Other personal medical history
- Family medical history
- Social history (including occupation, diet, physical activity, smoking, alternative medicine, exposure to pesticides and insecticides, zip code, Townsend Score of social deprivation)
- Previous imaging or diagnostic test results (e.g. ECHO, cardiac catheterisation, ECG, x-rays, CT scans, etc.)
- Other ad-hoc questions related to experience of cardiac complications, its treatment and participant reported outcomes
- Mortality
- Hospitalization rate
- Progression of disease
- EQ-5D-5L
- Jenkins Sleep Evaluation Questionnaire (JSEQ)
- Generalized Anxiety Disorder 2-item (GAD-2)
- Patient Health Questionnaire-2 (PHQ-2)
- Functional Assessment of Chronic Illness Therapy - Item GP5 (FACIT Item GP5)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Other outcome measures which may be included (see **Appendix 3**).

It is anticipated that many of these data fields will be automatically populated from EHR. Missing data will be captured by patient self-report. The maximum duration of administered questionnaires at any one time is not expected to exceed 20 minutes.

Depending on the 'sub-studies' that are linked to AccessCMD, participants may be invited to complete additional COAs. These may be self-reported or involve remote or in-person clinical assessment. A list of potential COAs is provided in **Appendix 3.**

After enrollment, participants may be invited to participate in additional research studies relating to CMD. These studies may be initiated by uMed, their academic partners, or independent academic and/or commercial entities. Participants will retain full control over their participation and how their data is used. Additional research will be conducted under a protocol amendment (or a separate protocol) and IRB approval, if it is not covered in this protocol and IRB approval.

Examples of additional research opportunities include:

1) **Longitudinal or cross-sectional observational studies**

- Questionnaires about CMD status are administered periodically.
- Questionnaires about CMD risk factors.
- Objective tests (ECG, ECHO)
- Virtual or in-person clinical assessments.

2) **Medical device studies** – for measuring symptoms of CMD or providing treatment.

3) **Clinical trials** - of approved or investigational medicinal products (using a traditional or decentralized model).

4) DNA collection and analysis

Participants may be invited to submit a saliva sample for DNA extraction and analysis. An at-home saliva sample collection kit will be dispatched in the mail to participants who consent to saliva collection and returned to a central lab for DNA extraction and storage.

Analysis (genotyping and/or sequencing) will take place at a CLIA-certified lab or lab accredited by the Standards Council of Canada (SCC). DNA can be shared with explicit consent with approved research collaborators to further understanding of CMD. Genotyping and/or sequencing data and clinical data may be shared in aggregated or de-aggregated forms, with approved collaborators to further understanding of CMD. Researchers receiving samples and/or data must have a written usage agreement. Samples will be stored for as long as deemed useful for research purposes.

8 REGISTRY SETTING

Engagement with participants will happen remotely and online. The initial approach will be made by an SMS message and/or email sent by uMed on behalf of the patient's Healthcare Provider (HCP) or Healthcare Institution (HCI) (+/- written material sent via mail), after identifying patients with a diagnosis of CMD from clinical records. Registration, information provision, consent to participate and research activities will all be managed online in a decentralized fashion.

9 SAMPLE AND RECRUITMENT

9.1 Inclusion criteria (see **Appendix 4**)

The principal goal of this project is to establish a core clinical dataset for CMD and to improve representativeness in CMD research. Hence the inclusion criteria are:

- All patients with a coded diagnosis of CMD +/- risk factors +/- additional prescription data.
- Aged ≥18 years old.
- Identified through a healthcare provider participating in AccessCMD in the US.
- Able to provide consent to participate.

9.2 Exclusion criteria

- Patients with dementia or receiving palliative/terminal care.
- Patients who have recorded a preference in their medical record that they do not wish to be considered for research or contacted regarding research opportunities.
- Patients who have recorded a preference not to share data for research.

9.3 Size of sample

Due to the aim of the project (i.e. to develop a new platform for research, establish a CCD for CMD and help facilitate access to research opportunities for patients with CMD, whilst improving equitability), the sample size will be as high as possible and is not based on statistical power calculations. Recruitment is currently planned in the UK, US, and Canada with an overall goal to enroll up to 10,000 individuals with CMD between those three countries.

9.4 Sampling technique

As above, the aim is to offer participation to all patients with a diagnosis of CMD identified through a healthcare provider participating in AccessCMD in the US and Canada.

9.5 Recruitment

Potential participants will be identified from EHR at HCIs who have elected to participate in AccessCMD.

9.6 Consent

This study will be conducted in accordance with the provisions of 21 CFR Part 50 (US) and the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (G-TCPS2) and Good Clinical Practice Integrated Addendum to E6 (R1). In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, details on how individuals' confidentiality will be maintained, and potential hazards/risks, will be presented to potential participants. Potential participants will be shown study information, including a list of frequently asked questions (FAQs). They will then view the HIPAA authorization information and FAQs. These will include contact details (email, phone) for the study support team in case of questions. Participants will check a box that they have read and understood the preceding sections and will enter their name and the date to provide consent and authorization (see appendix 6).

Capacity in clinical settings is decision-specific and assumed unless there is evidence to the contrary. It is unlikely that CMD patients with loss of capacity to participate in research would be actively responding to SMS messages inviting enrollment in a registry. However, the nature of data being collected and the non-invasiveness of the research undertaken in AccessCMD mean that there is minimal risk posed to participants.

Patients with dementia or receiving palliative/terminal care are automatically excluded from participating in the study. Recognizing that capacity may change, in a situation where loss of capacity exists the participant will be withdrawn from the registry. In the circumstance whereby carers or relatives wish to assist a participant in consenting by phone, confirmation that the patient has capacity to consent but requires assistance with the physical process or use of technology will be confirmed.

10 ETHICAL AND REGULATORY CONSIDERATIONS

The US Federal government passed the 21st Century Cures Act, which calls for researchers to incorporate the perspectives of patients into the development of trials, drugs, and devices in FDA's decision-making process. This law builds on the FDA's ongoing work to enhance researchers' ability to modernize clinical trial designs, including the use of real-world evidence and clinical outcome assessments, which will speed the development and review of novel medical products. Similarly, Canada's Roadmap for Open Science (2020) provides overarching principles to guide research activities in support of open science in Canada. These recommendations reflect Canada's commitment to working with international partners in developing open science policies, exploring supportive incentive structures, and identifying good practices for promoting increased access to the results of publicly funded research.

Selected examples of how the AccessPD protocol addresses the aims noted above are listed below.

Regulatory/ethical consideration	AccessCMD

Patients, service users and the public are given, and take, the opportunity to participate in health and social care research and to get involved in design, management, conduct & dissemination.	Patients, patient representatives and patient advocacy groups have been involved in the project design, scoping and priority setting. A PPI group will continue to advise as the project progresses (described in the relevant sections).
Safer, more efficient or more effective treatments, care and other services are developed and tested through ethical and scientifically sound research for the benefit of patients, service users and the public.	AccessCMD will enhance access for patients to research opportunities and the CMD research community to a unique dataset that combines clinical data and participant reported data. Together this will drive better understanding of etiology, manifestation, progression and potential therapeutic targets, as well as efficient recruitment for clinical trials.
Ensure that study populations better reflect the patient populations who could ultimately benefit from the research in clinical practice.	AccessCMD will enhance access for patients to research opportunities and make it easier for researchers to reach out to underserved populations. The use of clinical data also promotes more efficient recruitment of a diverse population and supports identification of participants for whom traditional referral centers are not accessible.
Researchers find it straightforward to do high-quality, ethical research.	AccessCMD will dramatically improve efficiency when it comes to identifying eligible participants for research and offering the opportunity to participants in a highly equitable manner.
Industry sees the US and Canada as great places to do health and social care research and increases its investment for the benefit of patients and service users.	Industry-led and academic-led research projects will be offered in the platform, increasing efficiency and breadth of opportunities, with increasing investment from those stakeholders.
Money from foundations and other research funders goes into carrying out research, not into navigating burdensome bureaucracy or duplicating previous work.	The AccessCMD model creates a platform which allows an ever growing dataset to be created and accessed by researchers. In doing so this dramatically reduces the cost and burden associated with creating bespoke programs that still remain the status quo.
Research projects get registered, the data and biosamples they collect can be made available for future analysis, with adequate consent and privacy safeguards, and research findings get published and summarized for those who took part in them.	AccessCMD is committed to an open science framework and sets a new standard for privacy safeguards by ensuring a broad based consent for secondary use of registry data is balanced through proactive engagement of specific secondary use projects. The platform also enables efficient sharing of publications and research summaries with participants.

10.1 Assessment and management of risk

Potential risks have been identified using the clinical risk management harm table in Appendix 7.

List of risks:

Risk	Describe the source of risk and the nature of the potential impact on individuals. Include associated compliance and corporate risks as necessary.	Likelihood	Impact	Overall Risk
1	External parties attempt to access data with malicious intent.	Low	Major	3
2	Malicious action by uMed employees to access, alter, or exploit data held on the registry system.	Low	Major	3
3	Patients receive an unwanted solicitation to engage in research.	Medium	Significant	2
4	A participant's health data is shared with a third-party organization using the registry system against their expectations or wishes.	Low	Significant	2
5	A participant is misidentified in communications leading to preferences and/or responses being associated with another record.	Medium	Significant	2
6	A third-party research group (e.g., a pharmaceutical company) that accesses sensitive data via the registry system utilizes this data for purposes beyond those stated in the data-sharing agreement.	Low	Major	3
7	Participant preferences listed in the registry conflict with those held by the participant's healthcare institution.	Medium	Minor	2
8	uMed fails to meet compliance requirements for information and security governance.	Low	Major	3
9	uMed becomes insolvent while holding sensitive data within the registry system.	Low	Significant	2
10	A change in privacy/data legislation invalidates registry system processes.	Low	Significant	2

Mitigating Actions

Risk	Options to reduce or eliminate risk	Effect on risk	Residual risk	Measure approved
1	Data is encrypted in transit and at rest and hosted in a certified Amazon Web Service (AWS) environment in line with US Code of Federal Regulations Title 45 CFR part 164 requirements, Canada's Personal Information Protection and Electronic Documents Act (PIPEDA) and the Personal Health Information Protection Act (Ontario, CA). The application is routinely penetration tested by an external party.	Reduced	Low	Yes
2	The registry system has implemented SOPs to address this risk including: ● Confidentiality Statements acknowledged by employees ● Prospective employee vetting ● Password Management SOP ● Assignment of unique identifier to employees to allow for tracking of access ● Two-factor authentication is in place to verify employee access. ● Actions on Employment Termination SOP ● An access control policy is in place as part of the acceptable use policy to manage the access of participants identifiable information and sensitive data.	Reduced	Low	Yes
3	All correspondence makes clear to the subject why they are being contacted and how to change preferences to prevent unwanted further correspondence.	Eliminated	Low	Yes
4	All patients must be consented to participate in the registry and for the data usage in the registry and sub-studies (Type A, B, C). The system will also ensure the data will not be shared if the participant has opted out.	Reduced	Low	Yes
5	The participant's identity will be confirmed before any consent is obtained. This is achieved by asking the participant to confirm the DOB, which is cross referenced with the DOB held against the record associated with the contact information in question. This contact information is obtained from the *HCI,* which supports another implicit layer of identity verification.	Reduced	Low	Yes

6	If the registry system is used to facilitate data sharing with a third party, access is only granted once the data sharing agreement is in place. Audit logs give an immutable record of activity and any access by named individuals within a 3rd party. E.g., DSAs, BAA, etc. Breach of this could result in legal action.	Reduced/ Accepted	Low	Yes
7	The registry system will record any participants who opt out of receiving contact and will inform the HCI.	Reduced	Low	Yes
8	In the event uMed becomes insolvent, all data created from participant engagement, including metadata and logs, will be returned to the provider organizations associated with their participant population. All copies of sensitive and personal data will be destroyed and access granted to *HCIs* and/or independent auditors to demonstrate this.	Eliminated	Low	Yes
9	uMed continuously reviews current and planned data legislation. If a change in data legislation is likely to affect uMed operations, then this will be highlighted alongside the mitigating measures planned by uMed to ensure ongoing compliance.	Reduced	Low	Yes
10	Policies are in place regarding the final disposal of electronically protected health information and the disposal of hardware/electronic media associated with the storage of such data.	Eliminated	Low	Yes
11	Policies and procedures are in place for responding to an emergency or other occurrence that damages systems that contain electronically protected health information. Procedures supporting data backup and recovery are in place, along with disaster recovery and Business Continuity Plan.	Reduced	Low	Yes

10.2 Potential Benefits

Participants will not benefit directly from being in this research study.

10.3 Institutional Review Board (IRB) and other Regulatory review & reports

This study will be conducted in accordance with the provisions of the US Code of Federal Regulations Title 21 and Canada's Food and Drug Regulations (CanadaFDR) and G-TCPS2. Before the start of the registry, uMed will seek central IRB approval, and as necessary, local IRB/REB approval, for the registry protocol, ICFs and other relevant documents (e.g. recruitment materials, advertisements). uMed will supply all necessary information for local IRB/REB submissions as necessary.

In addition:

- Substantial amendments that require review by an IRB/REB will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- All correspondence with the IRB/REB will be retained.
- It is the Principal Investigator's responsibility to produce the annual reports as required.
- The Principal Investigator will notify the IRB/REB of the end of the registry.
- An annual continuing review report will be submitted to the IRB/REB within 30 days of the anniversary date of the initial approval, and annually until the registry is declared ended.
- If the registry is ended prematurely, the Principal Investigator will notify the IRB/REB, including the reasons for the premature termination.
- Once the registry ends, the Principal Investigator will request closure of the study and submit a final report.

Regulatory Review & Compliance

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promoted by the International Conference on Harmonization (ICH), and any applicable national and local regulations including US FDA regulations under 21 CFR Parts 11, 46, 50 and 56 as applicable and Canada's FDR and Guidance Document for Clinical Trial Sponsors- Clinical Trial Applications (G-CanadaCTApps) guidance. Before any site can enroll participants into the registry, the Principal Investigator or designee will ensure that appropriate approvals from participating organizations are in place.

Amendments

For any amendment to the registry, the Principal 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. The Principal Investigator or designee will work with sites so they can obtain the necessary approvals for the amended protocol and implement the amendment.

Amendments to the protocol, Participant Information Sheet and ICFs will be made as required, for example, if the nature of information/data being collected from participants were to change. Amendments will be led and coordinated by the Principal Investigator (with support from administrative staff), and with the agreement of the sponsor (CS Ltd). The decision about when to make an amendment will be taken by the Principal Investigator, who will also determine whether the amendment is substantial or non-substantial, in consult with the IRB/REB. Amendments will be distributed via email to relevant stakeholders and the amendment history (along with all supporting documentation by version number and date) will be retained.

10.6 Protocol compliance

This protocol provides a written guide for the conduct of the project. Deviations from the protocol (if they occur) will be recorded by date, alongside a description of the deviation and will be available for audit.

10.7 Data privacy and participant confidentiality

A summary of the workflow and process of AccessCMD can be found in **Appendix 1**.

The core principle applied throughout AccessCMD is that Cohort Science is responsible for management of the data collected under the AccessCMD protocol. This data may be collected and managed by approved third party vendors that conform to the requirements of US Code of Federal

Regulations 45 CFR 164, Canada's PIPEDA and PrivAct privacy laws and Ontario Canada's Personal Health Information Protection Act. uMed assures that the privacy of subjects, including their personal identity and personal medical information, will be maintained at all times and ensures compliance with all privacy obligations under the US Health Insurance Portability and Accountability Act (HIPAA) and Ontario's Personal Health Information Protection Act (PHIPA). A business associate agreement (BAA) is established between the HCI and uMed (or any other appropriate third party) to ensure complete protection of PHI from all participants.

The BAA, allows the HCIs to participate in AccessCMD and for uMed to provide services to support delivery of studies. uMed therefore cannot use or share provider data with any third party without the permission from the HCI.

uMed transfers data to Cohort Science (the Sponsor) once a registry Participation Agreement is signed between Cohort Science and the HCI and the participant has consented to participate in the study and has given permission for the data transfer in line with requirements set out in the AccessCMD protocol. Prior to transfer of any registry data to Cohort Science (CS), permission of the HCI and participant consent will have been sought and obtained in line with the requirements of:

a. The AccessCMD protocol.
b. uMed:HCI BAA.

10.8 Data Retention

In accordance with HIPAA requirements and Canadian regulations, registry data will be retained for a minimum period of 7 (seven) years after the registry has been completed.

10.9 Access to the registry dataset

AccessCMD aims to create a sustainable registry model that incentivizes academic and commercial researchers to engage with the registry and develop new ideas, diagnostics and therapies that can improve the lives of patients with CMD.

Researchers will be provided access to the CCD once their credentials have been validated and a description of the intended project that will use the registry data has been provided to the registry management committee. The AccessCMD CCD includes:

a. Baseline and scheduled questionnaire data.
b. Linked clinical health record data.
c. Any additional data collected as part of a supported registry or sub-study where the funder of that registry/project has agreed for that data to be included in the open data.

In order to preserve incentives for industry engagement, Cohort Science or the funders of 'sub-studies' that capture additional data from registry participants will be able to request that access to this subset of data is restricted to specific users. Unless exceptional reasons are presented to the registry management committee, access to this additional data will not be restricted for more than 1 year after publication. After which, the previously restricted data will be made available as part of the CCD.

Importantly, participants associated with 'sub-studies' will be proactively engaged and presented information explaining who is funding the project and if access to data from this sub-study will be restricted. Participants are given a clear means to then opt out of further engagement with the 'sub-studies'.

10.10 Subject Withdrawals

Subjects will be advised in the informed consent that they have the right to withdraw from the study at any time without prejudice. If a participant wishes to leave AccessCMD, they may do this at any time without giving a reason by contacting the study team. Any data that has already been contributed to AccessCMD prior to their discontinuation will remain in the study database.

11 DISSEMINATION POLICY

11.1 Dissemination policy

- Cohort Science Ltd will manage and be responsible for the pseudonymised CCD.
- Any external researcher wishing to publish based on data from AccessPD will need approval from the registry management committee.
- Each patient enrolled in the study will receive quarterly newsletters updating them on the progress of AccessCMD, including the number of patients enrolled and high-level results from the study. It will also include information from scientific conferences and meetings where data from the study is being presented, medical publications of study data, research institutions who are partnering with AccessCMD and general updates on CMD.

11.2 Authorship eligibility guidelines and any intended use of professional writers

Cohort Science and uMed will be acknowledged as the sponsor and facilitating technology platform respectively in any publication using registry data.

12 REFERENCES

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3. Kivimäki M, Kuosma E, Ferrie JE, Luukkonen R, Nyberg ST, Alfredsson L, Batty GD, Brunner EJ, Fransson E, Goldberg M, Knutsson A, Koskenvuo M, Nordin M, Oksanen T, Pentti J, Rugulies R, Shipley MJ, Singh-Manoux A, Steptoe A, Suominen SB, Theorell T, Vahtera J, Virtanen M, Westerholm P, Westerlund H, Zins M, Hamer M, Bell JA, Tabak AG, Jokela M. Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe. Lancet Public Health. 2017 May 19;2(6):e277-e285. doi: 10.1016/S2468-2667(17)30074-9. PMID: 28626830; PMCID: PMC5463032.

13. APPENDICES

Appendix 1- AccessCMD: Summary of Workflow and Process
Appendix 2 – Governance of Sub-studies run within AccessCMD
Appendix 3 - Questionnaires and scales for 'sub-studies'
Appendix 4 - CMD ICD & SNOMED Codes
Appendix 5 - Schedule of Activities (Example)
Appendix 6- Consent process
Appendix 7 - Clinical Risk Management Harm Table

Appendix 1- AccessCMD: Summary of Workflow and Process

This document aims to provide a clear overview of the way in which participant data is collected and between Cohort Science and the HCIs used and participant engagement takes place as part of AccessCMD. References provided at the bottom of this document provide links to further detailed information.

Background:

- AccessCMD leverages a technology platform called uMed to support the targeted engagement of potential participants **on behalf of** the Healthcare Institution (HCI).
- uMed will institute independent data sharing agreements with HCIs that will enable providers to efficiently contact specific groups of patients based on searches of the medical record data held by the HCI.

Process Flow:

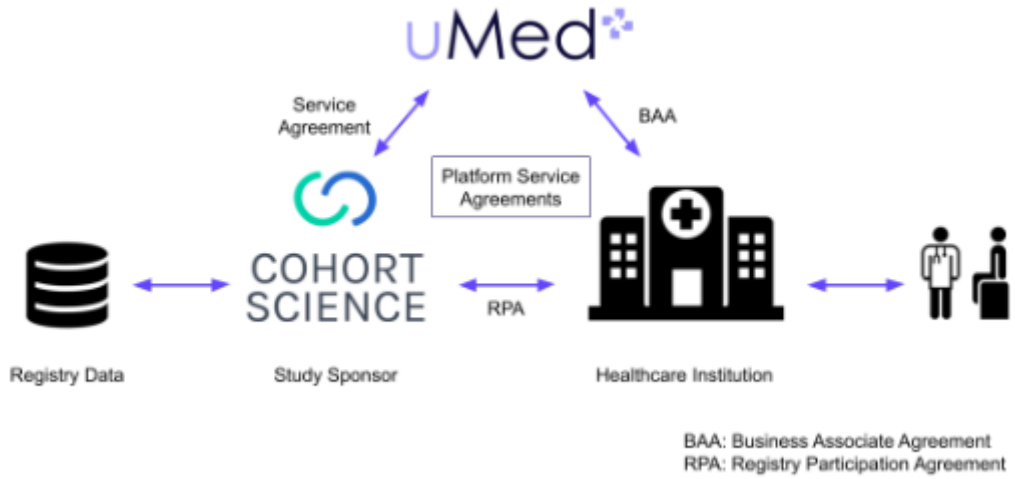

Figure A - Legal Relationships

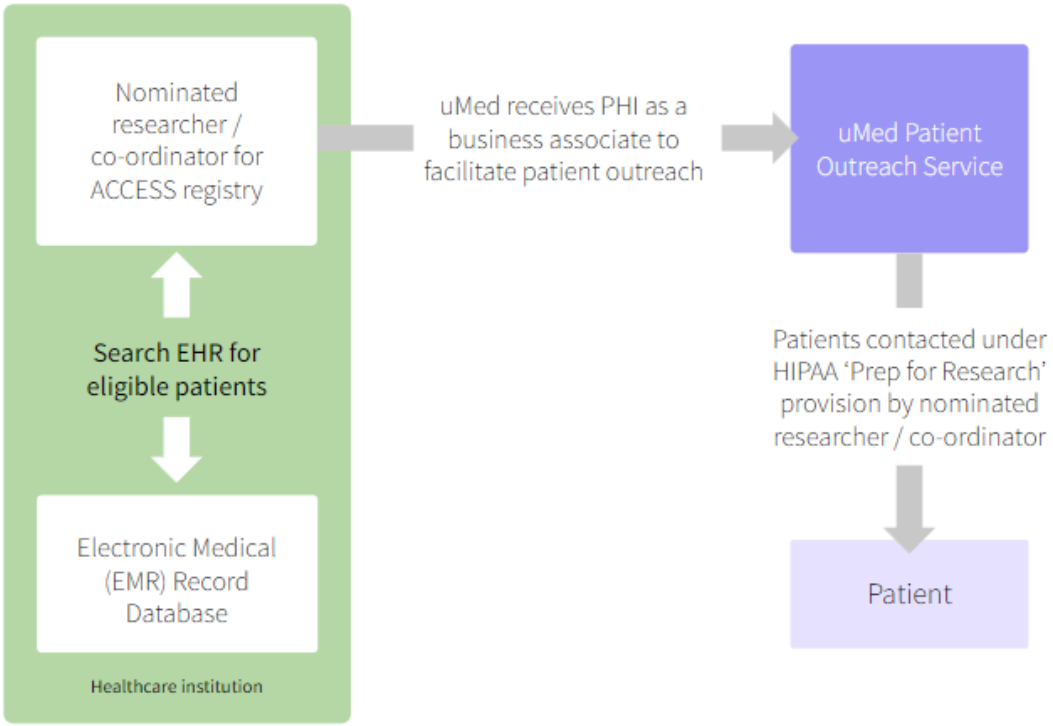

Figure B - Patient Outreach

Step 1:
uMed (uMed Technologies Inc) puts in place a Business Associate Agreement with a participating Healthcare Institution (HCI). This allows uMed to undertake tasks including patient outreach, engagement and support services for the HCIs under the 'healthcare operations' provision within HIPAA.

Step 2
The study sponsor (Cohort Science) enters into a study agreement with a HCI.

Step 3
uMed, with the approval and on behalf of the HCI, will contact potential participants and ask them to enroll in AccessCMD. This includes a link to study information and an electronic consent workflow. uMed acts on behalf of the provider to automate this outreach via text, email, and letter. The screenflow that potential participants receive can be viewed in Appendix 6. Once consented, Cohort Science will send participants study questionnaires and other outcome assessments as outlined in the protocol. Data collected from participants is consolidated with health record data.

Step 4
External researchers can engage with AccessCMD through 'sub-studies' which enables access for those external researchers to pseudonymised data and additional data collected from subgroups within the AccessCMD population to support analyses of specific research questions. All sub-studies that provide access to data will need to be approved by the AccessCMD Registry Management Committee. Further information on how access is managed can be found in section 8.8 of the protocol.

Appendix 2: Governance of Sub-studies run within AccessCMD

Sub-studies will be categorized into 3 types.
Type A: Sub-study using the existing pseudonymized study dataset
Type B: Sub-study requiring PROs, questionnaires or observational data that are already included in the protocol.
Type C: Sub-study requiring additional PROs, questionnaires or observational data that are not included in the protocol.

Type A Sub-studies will enable research teams external to AccessCMD to access the existing pseudonymized study dataset only. Access will be granted subject to review of the request by the AccessCMD management committee. As Type A sub-studies only utilize existing data and consent is already obtained for this secondary use, the participant does not need to opt-in.

Type B sub-studies are defined as those that will seek to capture PROs, questionnaires or observational data that are already included in the protocol. These sub-studies should not require a protocol amendment or IRB approval as new information is not being collected and the information will not be used in a way that is not described in the current protocol

Type C sub-studies are defined as those that will seek to capture additional PROs, questionnaires or observational data that are not included in the protocol. These sub-studies would be submitted as an amendment to the AccessCMD protocol with subsequent updated IRB approval. Participants within AccessCMD who wish to engage with the opportunity to be part of Type C sub-studies will be required to re-consent.

Note. Any interventional or clinical drug studies recruiting participants identified through AccessCMD will be conducted as standalone trials with their own protocols and will undertake independent IRB review prior to commencement.

Appendix 3 – Questionnaires and scales for 'sub-studies'

Name	Domain	Duration
EuroQoL 5D-5L (EQ-5D-5L)	HRQOL	1-2 minutes
Kansas City Cardiomyopathy Questionnaire (KCCQ)	Symptoms, HRQOL	4-6 minutes
Patient Health Questionnaire-2 (PHQ-2)	Mood	1-2 minutes
Generalized Anxiety Disorder 2-item (GAD-2)	Mood	1-2 minutes
Functional Assessment of Chronic Illness Therapy - Item GP5 (FACIT Item GP5)	HRQOL	1-2 minutes
Jenkins Sleep Evaluation Questionnaire- JSEQ	Sleep	1-2 minutes
Impact of Weight on Quality Of Life questionnaire (IWQOL-Lite)	HRQOL	1-2 minutes
BODY-Q	HRQOL	1-2 minutes
Medical Outcomes Short Form 12 (SF-12)	HRQOL	1-2 minutes
Appraisal of Diabetes Scale (ADS)	HRQOL	1-2 minutes
18-item Diabetes Health Profile (DHP-18)	HRQOL	1-2 minutes
Diabetes Quality-of-Life Brief Clinical Inventory (DQOL-BCI)	HRQOL	1-2 minutes
Problem Areas in Diabetes (PAID) questionnaire	HRQOL	1-2 minutes

Appendix 4- CMD ICD & SNOMED Codes

See supporting document.

Appendix 5- Schedule of Activities

Procedures	Screening	Baseline	Every 6 Months	Unscheduled
Informed consent	x			
Demographics (captured from patient and via EMR)		x	x	x
Medical history (captured from patient and via EMR)		x	x	x
PROs / Questionnaires • EuroQoL 5D-5L (EQ-5D-5L) • Kansas City Cardiomyopathy Questionnaire (KCCQ) • Patient Health Questionnaire-2 (PHQ-2) • Generalized Anxiety Disorder 2-item (GAD-2) • Functional Assessment of Chronic Illness Therapy - Item GP5 (FACIT Item GP5) • Jenkins Sleep Evaluation Questionnaire- JSEQ • Impact of Weight on Quality Of Life questionnaire (IWQOL-Lite) • BODY-Q • Medical Outcomes Short Form 12 (SF-12) • Appraisal of Diabetes Scale (ADS) • 18-item Diabetes Health Profile (DHP-18) • Diabetes Quality-of-Life Brief Clinical Inventory (DQOL-BCI) • Problem Areas in Diabetes (PAID) questionnaire		x	x	x
Supplementary PROs / Questionnaires				x
Contact for participation in 3rd party studies				x

Appendix 6 - Consent Process

See supporting document.

Appendix 7 - Clinical Risk Management Harm Table

Likelihood						
	Very High	3	4	4	5	5
	High	2	3	3	4	5
	Medium	2	2	3	3	4
	Low	1	2	2	3	4
	Very Low	1	1	2	2	3
		Minor	Significant	Considerable	Major	Catastrophic
		Impact				

Likelihood Category	Interpretation
Very high	Certain or almost certain; highly likely to occur
High	Not certain but very possible; reasonably expected to occur in most cases
Medium	Possible
Low	Could occur but in the great majority of occasions will not
Very low	Negligible or nearly negligible possibility of occurring

5	Unacceptable level of risk.
4	Mandatory elimination or control to reduce risk to an acceptable level
3	Undesirable level of risk Attempts should be made to eliminate or control to reduce risk to an acceptable level. Shall only be acceptable when further risk reduction is impractical.
2	Acceptable where cost of further reduction outweighs benefits gained.
1	Acceptable, no further action required

Consequence Classification	Interpretation	Number of Patients Affected
Catastrophic	Death	Multiple
	Permanent life-changing incapacity and any condition for which the prognosis is death or permanent life-changing incapacity; severe injury or severe incapacity from which recovery is not expected in the short term	Multiple
Major	Death	Single
	Permanent life-changing incapacity and any condition for which the prognosis is death or permanent life-changing incapacity; severe injury or severe incapacity from which recovery is not expected in the short term	Single
	Severe injury or severe incapacity from which recovery is expected in the short term	Multiple
	Severe psychological trauma	Multiple
Considerable	Severe injury or severe incapacity from which recovery is expected in the short term	Single
	Severe psychological trauma	Single
	Minor injury or injuries from which recovery is not expected in the short term.	Multiple
	Significant psychological trauma.	Multiple
Significant	Minor injury or injuries from which recovery is not expected in the short term.	Single
	Significant psychological trauma	Single
	Minor injury from which recovery is expected in the short term	Multiple
	Minor psychological upset; inconvenience	Multiple
Minor	Minor injury from which recovery is expected in the short term; minor psychological upset; inconvenience; any negligible severity	Single