PREDICT-TBI

(Prediction and Diagnosis using Imaging and Clinical biomarkers Trial in Traumatic Brain Injury)

Study Standard Operating Procedures:

Operation Manual

Version 7.0
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1 Overview

This PREDICT-TBI Study Operations Manual provides detailed information on PREDICT-TBI Study procedures. It is an essential tool that facilitates consistency in study protocol implementation across study sites. The purpose of this section of the manual is to provide PREDICT-TBI staff (PIs, AIs, Research Coordinators (RC)) at study sites with instructions that govern all aspects of the study including blood biospecimens, magnetic resonance imaging and outcome measurements.

PREDICT-TBI is a prospective, longitudinal, observational, multicentre study. Patients who have suffered a moderate or severe TBI, (as assessed by the Glasgow Coma Scale (GCS) and clinical record on hospital admission, or at the accident scene should the participant be intubated upon arrival to hospital) will be consecutively screened and recruited at each participating site. If a participant (or their Substitute Decision Maker (SDM) acting as the Person Responsible (PR) on their behalf) is unable or unwilling to undergo some study procedures, the study coordinator will collect the data from the procedures that they are willing to undergo. (See Appendix A for the PREDICT-TBI patient journey).

2 Study Participants and Recruitment

Participants with moderate to severe TBI will be recruited on hospital admission at participating sites in Australia. Severity of TBI is defined as (1):

- Moderate TBI is defined as a GCS score of 9-12
- Severe TBI is defined as a GCS score of ≤8

2.1 Inclusion Criteria

1. Aged ≥ 18 years old
2. Diagnosed with moderate or severe TBI*, with or without other injuries.

**TBI Definition – A TBI will be defined based on the post-resuscitation Glasgow Coma Scale (GCS) in the pre-hospital period and the first 24 hours of ICU admission, if admitted to ICU. Moderate and Severe TBI are defined by the following categories of GCS if in the opinion of the treating team GCS is not solely due to intoxication, sedation, or extracranial injury.*

2.2 Exclusion Criteria

1. Previous major stroke
2. Pregnancy, or may be pregnant
3. In the opinion of the investigator the participant would be unlikely to be able to comply with study procedures and follow up (e.g. lives overseas).
4. Presence of underlying disease with a life expectancy of less than 6 months
5. Known contraindication to MRI that will prevent study procedures
6. Patients who have suffered a devastating TBI with either progression towards brain death at the time of assessment or where the treating medical team are not committed to ongoing full supportive care
7. Traumatic brain injury occurred more than 72 hours ago

2.3 Informed Consent Timeline

Written and/or verbal informed consent will be sought from an SDM within a 5-day working period from the time the patient has been identified as being eligible for the study if one is available. Should

there be no SDM or patient consent within the 5-day working period, study data and biological samples relating to that participant will be destroyed commencing on working Day 6 from enrolment:

- Study data: All data will be removed from the REDCap database EXCEPT for the fields shown in "Appendix 8: REDCap Fields for Patients not Consented Within 5 Working Days", of the DCM.
- Biological Samples: Research Coordinators (RCs) are to notify the Clinical Trial Manager (CTM) and Assoc Prof Nasrallah which samples are to be destroyed. For samples stored onsite by the RCs, the RCs will destroy the samples and notify the CTM and Assoc Prof Nasrallah that the samples have been destroyed. For samples stored in pathology labs, the CTM or Assoc Prof Nasrallah will notify the lab to instruct them to destroy the samples. The CTM or Assoc Prof Nasrallah will then notify the site RCs that the instruction has been given to destroy the samples. This will be documented in REDCap as indicated in Appendix 8 of the DCM.

3 Schedule of Assessments

Study Timepoint Definition	**Timepoint 1: Up to within 36 hours of injury**	**Timepoint 2: Between 48 and 72 hours of injury**	**Days post injury +/- 24 hours**			**Acute/Post ICU**	**3 month post injury (+/- 14 days)**	**6 month post injury (+/- 21 days)**
			4	**7**	**14**			
Eligibility	**X**	**X**						
Clinical Outcome Measures							**X**	**X**
Clinical Imaging CT/MRI (if done)	**X**							
Study MRI						**X**	**X**	**X**
Blood Sampling	**X**	**X**	**X**				**X**	

4 Data Collection

All information will be recorded in non-identifiable form on REDCap, a secure web-based research data collection system or in the Research Data Manager at UQ, a collaborative, safe and secure large-scale storage facility to practice good stewardship of research data.

In REDCap, each patient will be given a specific ID with the following nomenclature:

Study	**Site**	**Subject ID**
PR-TBI	01	001-299

For example: PR-TBI-01-001

Where Sites are coded based on the following:

- 01 = The Royal Brisbane and Women's Hospital (RBWH)
- 02 = The Princess Alexandra Hospital (PAH)
- 03 = Royal Darwin Hospital (RDH)
- 04 = Liverpool Hospital (LH)
- 05 = Gold Coast University Hospital (GCUH)
- 06 = Townsville University Hospital (TUH)
- 07 = The Alfred Hospital

The following information will be collected for each participant from source data. Clinical Data will be recorded at the time of hospital admission to pre-ICU admission. Day 1 data collection will commence from admission to ICU/HDU/Ward (data may only be recorded for a partial day, depending on time of admission). Clinical data will continue to be collected for up to 14 days (midnight to midnight) while the patient is still in the intensive care unit.

Data collected for all participants for study purposes	
Demographics	age, sex, height, weight, handedness, pre-morbid work status, living arrangement, education level, postcode, discharge destination type, date and cause of death (if applicable)
Study consent documentation	Informed consent date, document if by participant or a Person Responsible, study withdrawal date, document if by participant or Person Responsible.
Past medical history	APACHE score, co-morbidities, significant past medical history, mental health history, history of regular substance abuse
Current medical condition	Severity of TBI, other injury types, ISS code, date of injury, time of injury, mode of injury
Clinical records and measures	Objective physiological criteria recorded automatically from the electronic physiological monitoring system - Glasgow Coma Scale, APACHE score, Blood pressure, temperature, pulse rate, intracranial pressure (ICP) level, pupil reactions, blood oxygen levels, brainstem reflexes, intubation and extubation dates, complications (such as infections), treatments for complications
Clinical treatments	Surgery date and type, raised ICP interventions, tracheostomy insertion/removal dates
Imaging	CT images and reports, MRI images and reports
Rehabilitation	Rehabilitation start date, type of rehabilitation received e.g., speech therapy, physiotherapy
Length of Stay (LOS)	LOS in ICU, acute care, inpatient rehabilitation and whole hospital LOS
Protocol Deviations	Date, time, description, action taken
AE/SAE/SUSAR	Date, time, description, action taken
Outcome measures	GOS-E, PROMIS, PCL-5, GAD-7, PHQ-15, PHQ-9, BRS, BRISC

*Please refer to the PREDICT-TBI Data Completion Manual for detailed description of all the data elements to be collected as part of the study.

5 Blood Sampling Procedures

5.1 Blood Sample Study Collection Kits

Collection and processing tubes will be supplied to each site in the form of a kit with tube labels and pathology request form relevant to each site included. Samples will be labelled in the following nomenclature:

Study	Site	Subject ID	Blood Draw	Specimen Vial
PR-TBI	01	001-299	*TP1-TPn* TP1=First sample at timepoint 1 TP2=Second sample at timepoint 2 … TPn=nth sample at timepoint n	E1 (ETDA 1) E2 (EDTA 2) S (SST)

For example: PR-TBI-01-001-TPI-E1 ← SPECIMEN VIAL

PREDICT-TBI SITE PATIENT ID BLOOD DRAW

Each patient will have six kits in total, one for each timepoint of blood collection. Each site will be provided with the below kits from QBI:

- 2 x 10ml EDTA tubes
- 1 x 5ml SST tube
- 1 x 5ml serology tube
- 10 x 1.5 ml tubes
- 1 x specimen bags
- Study labels

Each tube will be labelled as below:

1. E1: 1st EDTA blood collection of 10 ml
2. E2: 2nd EDTA blood collection of 10 ml
3. S: 5.0 ml blood collection
4. E1-a: 1.5 ml plasma after processing from EDTA1
5. E1-b: 1.5 ml plasma after processing from EDTA1
6. E1-c: 1.5 ml plasma after processing from EDTA1
7. E1-d: 1.5 ml plasma after processing from EDTA1
8. E1-RC: 1.5 ml tube for red blood cells of EDTA1
9. E2-a: 1.5 ml plasma after processing from EDTA2
10. E2-b: 1.5 ml plasma after processing from EDTA2
11. E2-c: 1.5 ml plasma after processing from EDTA2
12. E2-d: 1.5 ml plasma after processing from EDTA2
13. E2-RC: 1.5 ml tube for red blood cells of EDTA2
14. S-1: 3.0 ml tube for Plasma deriving from SST tube after processing

Write on the labels with a ballpoint pen and place labels on ALL serum and aliquot tubes BEFORE any sample collection, processing or freezing - this should help ensure that the label adheres to the tube before exposure to moisture or different temperatures. Labels need to be fixed horizontally (wrapped around sideways if the tube is upright) so that they can be read while standing the tube on its base and placed just below the ridges of the aliquot tube. Please take a moment to ensure that the label is completely adherent to each tube. Sample boxes will be labelled with the study and site name and the box number (e.g., PREDICT-TBI-TUH-01).

All samples will be stored at the hospital pathology storage facility with study labels provided by QBI. The label will also include the Date and Time that the sample was drawn. Finalised samples are to be placed immediately into a rack in an esky on dry ice and then transferred to the hospital pathology laboratories where they will be stored at -80°C.

Please be sure to order additional kits before you run out, so you are prepared for both scheduled sampling and new patients. Please allow at least 15 days for additional kits to be delivered.

5.2 Blood Sample Timepoints

Blood samples will be collected at the time points as per this schedule.
Important note: please do not collect samples from Friday at 1600hr through to Monday at 0400hrs, even if this means that the first sample (within 24 hours of injury) is missed. Samples cannot be processed over the weekends and are not able to be stored for more than 8 hours prior to processing. All other sample timepoints should be timed for a weekday collection.

All information related to blood sample collection must be recorded in REDCap, "13. Study Blood Samples", at each time-point, including missed samples.

Blood Sample Scheduling		
TIMEPOINT	TEST IF INPATIENT	TEST IF OUTPATIENT
Timepoint 1 (within 36 hours of injury)	✓	✗
Then on the following days		
Timepoint 2 (between 48- and 72-hours post injury)	✓	✗
If patients are not enrolled by 72 hours post injury, patients are no longer eligible for the study.		
Timepoint 3 (Day 4 post injury + 24hours)	✓	✗
Timepoint 4 (Day 7 post injury +/- 24hours)	✓	✗
Timepoint 5 (Day 14 post injury +/- 24hours)	✓	✗
STOP then:		
*3 months post injury (+/- 14 days)	✓	✓
*6 months post injury (+/- 14 days)	✗	✗

- **Blood Sampling during inpatient stay**

The Research Coordinator will inform the participant, and if applicable their carer, of when to expect study bloods to be taken and how this will happen. Study bloods will be taken by qualified staff, either registered nurses with venepuncture training or phlebotomists. If the participant is in ICU and has a central/arterial line, blood will be drawn using that line to minimise invasive procedures.

- **Blood Sampling for outpatients**

The Research Coordinator will contact the participant to arrange for blood samples to be taken either on the day of a study MRI, or if no study MRI is being done, at 3-months post injury. If the participant is undergoing MRI, study bloods should be taken on the same day, **prior** to the MRI scan.

5.3 Materials and Equipment Required at the Study Site for Local Processing Prior to Shipping

The following materials and equipment are necessary for the processing of specimens at the collection site and are to be **supplied by the local site**:

- Personal Protective Equipment
- Tourniquet
- SST tubes
- Cleansing Prep Pad
- Gauze Pad
- Bandage
- Needles
- Microcentrifuge tube rack
- Gloves
- Sharps bin and lid

5.4 Transport of Plasma Samples

Samples will be collected by a specialist courier company which will be arranged by QBI and shipped on dry ice to QBI at the expense of UQ.

To arrange for the packaging and transport of samples, please contact the Trial Research Manager, at predict-tbi@uq.edu.au

For PAH specific details see Appendix B

Transport of plasma samples to QBI will occur as follows:

- Samples will remain housed in their boxes during sample transport
- Electronic copies of the completed Biospecimen Record Summary and Shipment Notifications shall be sent to QBI
- The courier will collect all samples at the request of the site study coordinator
- The courier will provide all packing materials.
- The courier will pack samples to be compliant with IATA requirements.

5.5 Shipping Frequency and Conditions

Frequency of shipments will depend on the enrolment rate and on the storage capacity of the hospital laboratory at each study site. Frozen samples should be shipped at least quarterly. Please ensure adequate storage at -80°C prior to shipment. Check the weather report to make sure that impending weather events (hurricanes etc) will not impact shipping of delivery of the samples.

- **Shipping Days**

QBI: Frozen Samples must be shipped on Mondays, Tuesdays, or Wednesdays only to allow them to be received during the week.

- **Holiday Schedules**

Please be sure to verify with the courier's schedule prior to shipping close to a public holiday. This chart represents national public holidays, please be aware of any state public holidays which may impact shipping or receiving of samples.

New Year's Day	1 January
Australia Day	26 January
Good Friday	Varies
Easter Monday	Varies
ANZAC Day	25 April
Christmas Day	25 December
Boxing Day	26 December

Additionally, UQ is closed from the 25th of December till the 2nd of January each year. Do not ship any samples during these periods.

5.6 Management of blood samples if absence/withdrawal of consent

Samples from patients where consent to participate in the study has been revoked, and they have withdrawn from blood analysis, should be destroyed at participating sites. Data from patients where consent to participate in the study has been revoked, and they have withdrawn from their data being used, should be deleted in REDCap, EXCEPT for the fields indicated in Appendix 8 of the DCM. This will be documented in REDCap.

Only samples that have written or verbal consent obtained should be transferred to QBI.

5.7 Deviations from Prescribed Sample Collection and Storage

The following may each be considered a deviation from the PREDICT TBI study Protocol:
- samples are collected outside of the prescribed collection times
- samples have not been processed and/or stored as outlined in this Operations Manual

In each of the above circumstances, the samples may still be valid, however, the following will need to be completed:
- document the reason for this deviation in REDCap
- notify the Trial Research Manager

Please do not destroy samples – send to QBI as per normal process.
Note: the above deviations DO NOT require to be reported as protocol deviations for the main PREDICT-TBI study.

5.8 Safety Reporting

In this sub-study, adverse events are likely to be extremely rare due to a lack of intervention. However, it is possible for adverse events to arise from the interactions required for participation in the study (i.e., directly resulting from the procedure of blood collection) and these will be reportable to the coordinating centre and local ethics committee where applicable.

Clinically significant procedural related adverse events will be reported on the relevant form and submitted to the Central Coordinating Centre within 72 hours. These will be reviewed by the coordinating centre staff and recorded in a safety database. These will also be recorded in REDCap, "18. AE/SAE/SUSAR".

Only those reactions that are thought to have a direct causal relationship with the PREDICT-TBI study procedures should be reported as an Adverse Event (AE).

Reporting requirements:
AEs including serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be reported from the time of enrolment into the PREDICT-TBI study until completion of the trial.

5.9 Monitoring

Study monitoring will be conducted with a focus on study sampling and sample integrity as follows:

Study Sampling:

- Confirm consent for sample collection
- On site – verify study procedures are performed in accordance to the protocol and recorded in REDCap according to the Biospecimen SOP.
- Remotely – verify study procedures are performed in accordance to the protocol and recorded in REDCap according to the Biospecimen SOP.

5.10 Sample Integrity

- Confirm that each site has the capacity to store samples in a monitored -70 °C to -80 °C freezer
- Verify freezer log if available
- Confirm all samples have been processed and stored according to the protocol
- If there has been a storage failure, a note to file must be recorded in the site folder outlining subject number and explaining the situation and a copy forwarded to the project manager.

*Please refer to the Standard Operating Manual for the PREDICT-TBI Blood Biospecimen for detailed description of all the associated methods, collection, processing, storage, transfer, and archiving of the blood biospecimens for this study.

6 Imaging

6.1 Neuroimaging Contacts

Name	Contact details	Responsibility
Fatima Nasrallah	f.nasrallah@uq.edu.au	Lead Neuroimaging Investigator – all trial related enquiries- data acquisition, data archiving
Aswin Narayanan	a.narayanan@uq.edu.au	Data management – all data transfer and archiving related enquiries
Katie McMahon	k21.mcmahon@qut.edu.a	Data Acquisition – sequence related enquiries

6.2 MRI Timepoints

In this study, advanced MRIs will be performed up to three times for each patient at the following timepoints:

1.	Post ICU/HDU Discharge
2.	3 months post injury (± 14 days)
3.	6 months post injury (± 21 days)

**Note: For those participants who have reached 8 weeks post injury and have not been able to have the post ICU discharge MRI scan, (i.e., not met MRI criteria or are still an ICU in-patient), only two MRI scans will be done: the first one will occur anytime between post ICU discharge and the 3-month timepoint and at 6 months post injury.*

6.3 MRI Contraindications

All participants will be medically assessed with regards to their suitability to undergo study MRI, both when the MRI is organised and on the day of the MRI scan.

The following are **contraindications** for MRI:

- Neurosurgery leading to the insertion of coils or clips
- Cardiac interventions with artificial heart valves, cardiac stents, pacemakers, defibrillator, loop recorders
- Ear implants (Stapes or Cochlear implants)
- Neuro-stimulators (spinal or deep brain)
- Implanted drug infusion pumps
- Shunts (programable valves, ventriculoperitoneal or spinal)
- Bullets or shrapnel injury
- Tissue expanders
- Claustrophobia
- Contrast allergy

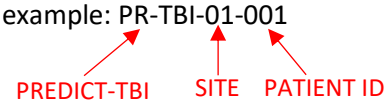
- Renal failure: serum creatinine of estimated glomerular filtration rate (eGFR) must be recorded in the last 3 months as <30mL/min. Patients must not be on dialysis.
- Morbid obesity
- Non-removable items such as fixed dentures, medication patches on the skin or body piercings.

6.4 MRI Data Labelling

On the Scanner, each patient will be given a specific ID with the following nomenclature:

Study	Site	Subject ID
PR-TBI	01	001-299

For example: PR-TBI-01-001



6.5 MRI Process

Participant safety is paramount. All site-specific approved MRI procedures will be followed. The Research Coordinator's (RC) role is to provide information, orientation, reassurance and ensure that the participants experience of this study procedure is as positive as possible.

Before the MRI	The RC will liaise with the participant and/or their carer to ascertain that the participant is willing to have an MRI scan. Please note that anyone accompanying the patient, such as a carer or next of kin, will also need to undergo the MRI checklist. The RC will discuss suitable days/times for the participant to attend with the participant and/or their carer and (if the participant is an inpatient) clinical staff The RC will arrange a date and time that is suitable for the participant to attend MRI - MRI sequence approximately 40 minutes The participant's MRI suitability to be assessed as per study site MRI protocol/guidelines Participant must have been discharged from ICU Participant must have cardiovascular and haemodynamic stability Participant must not be agitated and must be able to cooperate (the ability to lie still and remain flat for the procedure is essential for the examination). Participant must not require sedation Participant will be transported to the scanner Participant has (if any) only modest oxygen requirement (<50% inspired oxygen concentration)

	Participants must be re-screened for MRI contraindications immediately before the MRI scan. MRI appointment to be coincided with clinical outpatient appointments if possible For the 3-month post injury timepoint the RC is to arrange for study blood samples will be taken on the same day as the MRI, **BEFORE** the MRI procedure The RC will inform the participant and/or carer of the date and time of the procedure. Project Manager will make any necessary travel/accommodation/meal voucher arrangements The RC will explain the procedure (what to expect and timing) address concerns and provide reassurance. See Appendix C as an example of information provided to people undergoing MRI The RC will show the participant and carer where the toilets are located and provide the participant with the opportunity to use the toilet before the scan begins If the participant has a nasogastric feeding tube in situ it should be in free drainage to minimize risk of gastric reflux and aspiration whilst lying flat on the magnet If possible, if infusions are running and cannot be paused during the MRI, MRI compatible pumps are required. Alternatively, long intravenous (IV) extensions are used to allow non-MRI compatible pumps to be used located outside the MRI room
During the MRI	The RC to be available to the participant/carer throughout their attendance for the MRI procedure Participants will be provided with a way of communicating during the scan (buzzer or similar) Participants can ask for the scan to be paused or stopped completely at any time during the scan Noise cancelling and/or audio distraction equipment will be provided An intravenous cannula for contrast administration will be inserted by a member of the medical team MRI sequences will be hierarchised in order of priority Participants will be instructed to open their eyes during the fMRI sequence Standard hospital response systems are available throughout the procedure Use standard local practice for monitoring the participant during the scan will be used - these may include devices to monitor pulse and O2 levels

Following the MRI	Any questions or concerns that the participant and carer have will be addressed The RC will accompany the participant and carer to their ward or to their transport A clinical MRI report will be uploaded to the hospital medical record Any incidental findings will be reported by the radiology team and reviewed by the participants treating team

6.6 Inpatient MRI Process

The following information is specific to study participants undergoing study MRI during their INPATIENT stay:

- The RC will liaise with the medical team according to local hospital policy for the participant to attend a study MRI scan
- The MRI will be booked by the RC once medical approval granted
- The scheduled study-MRI will be documented in participant's medical chart. The treating medical team and ward nurse manager will be notified by the RC of the date and time of the scan.
- The RC will arrange for study bloods to be drawn on the morning of the scan
- The participant (and carer if applicable) will be escorted by the RC and a ward nurse to the imaging department
- The participant's identity will be checked by the RC and ward nurse
- Identity check will also be performed prior to the MRI by imaging staff.
- At conclusion of the MRI, the radiology staff and RC will notify ward staff that the participant is ready to return to the ward.
- The participant will be escorted back to the ward according to local hospital policy.

6.7 Outpatient MRI Process

The following information is specific for study participants undergoing MRI as OUTPATIENTS.

The participant will be escorted by the RC from the time they arrive at the hospital/imaging facility until the conclusion of all study procedures, including escorting them back to their transport. If the participant is traveling to have the MRI from their usual place of residence, arrangements may include:

- Liaison with the participant and/or carer about their needs
- Liaison with a residential rehabilitation facility staff about the participant's needs
- Liaison with imaging staff about the participant's needs
- Calling the participant/carer/residential facility the week before, the day before and possibly the day of the MRI as a reminder of the procedure

Project Manager will be responsible for organising:

- Organisation of transport
- Organisation of accommodation
- Organisation of meal vouchers

6.8 MRIs Ordered for Clinical Indications

Some participants may have CT scans and/or MRIs ordered for standard clinical indications. In these situations, the RC will organise for these images and reports to be uploaded into the study database and RDM.

6.9 Safety Reporting

In this study, adverse events are likely to be rare as there is no medical intervention beyond blood sample collection and MRI scans, which will include the use of Contrast. However, it is possible for adverse events to arise from the interactions required for participation in the study (for example, a reaction to the Contrast solution) and these will be reportable to the Central Coordinating Centre (UQ) and local ethics committee where applicable. Clinically significant procedural related adverse events will be reported and submitted to the Central Coordinating Centre within 72 hours. These will be reviewed by the coordinating centre staff and recorded in a safety database. Only those reactions that are thought to have a direct causal relationship with the study procedures should be reported as an Adverse Event (AE). These will also be recorded in REDCap, "18. AE/SAE/SUSAR".

*Please refer to the Standard Operating Manual for the Imaging for detailed description of the MRI procedures, MRI acquisition details, transfer of data and storage related to this study

6.10 Sending MRI Report to Participant's GP

If a participant requests a copy of their MRI Report, this should be sent to the participant's GP accompanied by the PREDICT-TBI MRI Report Letter to GP (See Appendix D).
Please note: MRI reports cannot be sent directly to the participant and are only required to be sent if the participant requests a copy.

7 Neurological Outcome Measures

Neurological outcomes measures will be administered by the RC at each of the sites either by phone or face-to-face. Caregivers can assist and/or provide responses if the participant does not have capacity.

Neurological Outcome Measures								
TIMEPOINT	GOS-E	PROMIS	PCL-5	GAD-7	PHQ-15	PHQ-9	BRS	BRISC
3 months post injury	✓	✓	✓	✓	✓	✓	✓	
6 months post injury	✓	✓	✓	✓	✓	✓	✓	✓

- Glasgow Outcome Scale – Extended (GOSE)
- Patient Reported Outcome Measurement Information System (PROMIS)
- Post-Traumatic Stress Disorder Checklist) PCL-5
- Generalized Anxiety Disorder 7-item Scale (GAD-7)
- Patient Health Assessment - 15 (PHQ-15)
- Patient Health Assessment - 9 (PHQ-9)
- Brief Resilience Scale (BRS)
- Barry Rehabilitation Inpatient Screening of Cognition (BRISC)

7.1 Outcome Measurement Execution

There may be times that a participant is unable or unwilling to attend for in-person assessments. All assessments can be executed by phone or in person, or a mixture of both.

The RC will assess each participant's situation to decide what the most appropriate method is and whether the assessments can be answered by the participant themselves, their Relative/Friend/Caretaker alone or a combination of both.

The Outcome Measurement assessments are recorded by the site RC and transcribed onto the eCRF (REDCap) with a record of the date of each assessment and:

- Whether the assessment was carried out in person, over the phone or other method
- Whether responses were from the Participant alone, Relative/Friend/Caretaker alone or Participant plus Relative/Friend/Caretaker.

Do not record any identifying information on REDCap.

There is a window either side of each time point (Refer to Study Protocol: Section 15) to allow flexibility for participant availability and fatigue. The Outcome Measures may be recorded over different days, as close to the 3- or 6-month post injury time point as possible, and all Outcome Measure assessments for any one timepoint should be recorded within 7 working days of each other.

If the examiner suspects or encounters difficulty scheduling the in-person visit within the appropriate assessment window, every effort should be made to obtain these measures by phone within the window timeframe. If the participant is going to have study bloods and/or MRI done at 3 and/or 6 months post injury the Outcome Measures should be recorded on or as close as possible to the day these are done.

7.2 General Assessment Administration Guidelines

The goal of the PREDICT-TBI Outcome Assessments is to use standardized assessments to objectively and reliably assess the participant's functional status, cognitive abilities, mental health, social participation, quality of life, and the economic impact of the injury without placing undue burden on the participant. Because the RC can influence results to some degree even when standardized procedures are used, it is desirable to have the same RC conduct all assessments during the course of this protocol.

Before executing the assessments, the RC should liaise with the participant and/or carer about their ability to hear and see and make sure the participant is wearing (if needed) corrective eyeglasses and/or hearing aids. It is permissible to repeat the instructions and questions as needed. The RC should use his/her judgment in deciding when it is necessary to repeat instructions, questions and response options. This will vary across participants.

The skill and judgment of the RC often affects the participant's willingness to be assessed and the effort he/she invests. Thus, during an actual assessment session the RC must observe and assess participant behaviour and make necessary adjustments.

7.3 Scheduling and Coordinating Follow Up Appointments

Consent to conduct follow-up outcome assessments was obtained at the time of study enrolment, so no additional consent is required. Sites may wish to schedule all follow-up assessments when participants are first enrolled in the study but will need confirm the participant's location and place reminder calls approximately 3 weeks in advance of each follow-up assessment date. It is also permissible to defer scheduling the 3- and 6-month follow-ups until closer to the time they are due.

Participants should be informed that all study procedures, including Outcome Assessments, should not impact their normal prescribed medication schedule.

A minimum of two appointment reminders should be sent by mail, email, text, or telephone call, the second occurring 24 hours before the scheduled visit. The RC needs to make all efforts to make sure that the participant will attend the follow-up session including working out the details of the logistics of travel (if the participant is attending in person), who will accompany the participant (if applicable), even calling them the morning of the assessment session to re-confirm their attendance.

In cases of "no shows", the RC should continue to attempt to reach the participant to perform the outcome evaluation for that particular follow-up timepoint (Refer to Study Protocol: Section 15). If the participant does not complete the follow-up assessment within the pre-specified assessment window of the target follow-up date, this follow-up assessment should be considered missed, unless rearranged (Refer to Study Protocol: Section 14.3). All points of contact should be documented in the eCRF in REDCap.

To avoid undue fatigue on the day of the scheduled assessment, every effort should be made to conduct the assessments in the morning, before the participant engages in other required study visit activities if planned (e.g. imaging, blood draws). If the outcome assessments cannot be completed prior to all other study visit activities, the RC should ensure that the participant is given an adequate break, including snack or drink, before engaging or re-engaging the participant in completing the Outcome Assessments.

7.4 Outcome Measurement Timing Deviation

In a situation where the windows close before all of the Outcome Measures have been obtained, and the participant indicates willingness to complete the assessments, the outcome measures should still be recorded but the RC must email the PREDICT TBI Study Coordinator with a brief description of the circumstances that led to the delay and the anticipated date for the completion of these measures and this information should also be recorded In REDCap.

7.5 Conducting Outcome Assessments in the Inpatient Setting

All sites should set up a local process to coordinate outcome assessments for participants who are still in the inpatient setting at the time outcome measure assessments. The site PI and RC should establish a procedure that enables the RC to work with the participant's treating physician and clinical staff to arrange and conduct the follow-up assessments on the ward. Before attempting to conduct the assessment, the RC should speak with the appropriate clinical personnel to:

1. Obtain medical approval to perform the assessments
2. Determine if there are precautions that need to be implemented (e.g. Personal Protective Equipment)

7.6 Establishing Rapport and Provision of General Instructions

The RC should begin the assessment session by introducing him/herself by name and explaining his/her role. The RC should describe the following:

- The purpose of the assessments
- What the assessments will be like
- How long the assessments are likely to take
- That the participant may take breaks

The participant should be given an opportunity to ask questions and every effort should be made to place the individual at ease. If the participant is able and willing to provide responses themselves family members should be instructed to avoid making any comments during the assessments.

The RC should read the questions out and allow the participant to see and mark the form as independently as possible. The RC may also record the responses for the participant if necessary.

It is the RC's responsibility to ensure that the participant understands the questions and that understanding is maintained throughout the assessments. Instructions may be repeated, and clarifications provided. If there are questions, which in the RC's opinion may cause distress to the participant, these questions can be asked later or missed completely.

7.7 Maintaining Participant Focus During Assessments

Some participants may interrupt assessments to engage in social conversation or become distracted in other ways. In these cases, the examiner should politely "re-orient" the participant back to the assessment. If the assessment order (Refer to Section 4.10) cannot be adhered to for any reason, the RC should make note of the circumstances.

7.8 Provision of Feedback During Assessments

Should the participant request feedback regarding his/her answers, only neutral feedback should be provided (e.g. "you are doing fine."). Good effort should be reinforced, and the RC should give no indication that answers are right or wrong. Should the participant give more than one answer, ask that the "best" answer be provided, without cueing for a specific response. "Which one is it?" can be a useful prompt to get a participant to choose a single answer. If the participant gives an unclear or ambiguous response, request clarification rather than guessing at the intended response. Participants should be encouraged to give an answer even if they are unsure. "What's your best answer?" can be a helpful prompt.

If the participant expresses or exhibits signs of frustration, or requests that the assessments be discontinued, the examiner should acknowledge the participant's concerns, and take note of any reported or expressed physical symptoms (e.g. pain, fatigue) that could be interfering with the participant's ability to tolerate the assessments. If in the RC's judgment, it may be possible to continue the assessment one attempt should be made to do so.

The participant should not, under any circumstances, be pressed to continue the assessment as this may precipitate agitation, invalidate results and/or decrease the probability of him/her returning for future assessments.

Whether a participant is fatigued, frustrated or merely distracted, there is not one approach that will work with all participants, but the RC should acknowledge the participant's concerns, consider the probability that the participant can be re-directed to the assessment and proceed accordingly to continue or re-schedule.

7.9 Assessment Completion in REDCap

Record in REDCap if the measure was completed in full, partly completed (and the reason why it was partly completed) or not completed.

7.10 Confounding Factors Management

If the RC identifies a confounding factor that he or she believes may have influenced the outcome assessment scoring (e.g. under the influence of illicit substances, effects of a new illness or injury, emotional lability, etc), a narrative description of the confounding circumstance should be recorded under comments in the Outcomes section in REDCap

7.11 Incidental Findings Management

During the execution of these assessments it is possible that the participant or their carer shares information about the participant's health, well-being, safety or other concern which may not already be known by their treating team, with the RC. The participant will be under either inpatient care or outpatient follow up. Should concerns about the participant's situation or condition become apparent during the assessment process this information will be discussed with and reviewed by the participant's treating physician.

7.12 Withdrawal of Consent

Should the participant (or their Person Responsible if applicable) withdraw consent to continue their involvement in the study, the RC and/or PI may discuss the reasons for this with the participant. If it is possible to address their concerns, their decision to withdraw or continue on the study can be reviewed by the study personnel with the participant.

Should the participant confirm their desire to withdraw, the PI or RC must confirm if they wish to withdraw from the entire study or from the Outcome Measure Assessments component only, and document and act upon this decision.

7.13 Retention of Source Documents

The Outcome Assessments will be completed on paper copies of the questionnaires and then transcribed onto the eCRF by the RC. The paper copies should be identified only with the participant's ID number, date of the assessment, method of completion, respondent and the study timepoint and filed locally, with the signed PICF and stored in a secure locked location.

*Please refer to the Standard Operating Manual for the Neurological Outcome Measures for detailed description of the Measures that need to be conducted for each patient.

8 Study withdrawal

The participant may withdraw their consent to participate in the study AT ANY POINT, they do not need to provide a reason for this. During their enrolment participants may also decide to only take part in some study procedures but not all.
The RC or delegate will:

1. Ask their (or the PR) permission to retain study data collected to date
2. Document this in the electronic CRF and action their decision
3. Inform the Principal Investigator
4. Inform the coordinating study centre coordinator
5. Provide the participant (or the PR) with a copy of the signed study withdrawal form, file the original in the site trial file and place a copy in the participant's medical chart

If the participant (or PR) declines to have their study data retained and used for study analysis, the coordinating centre will ensure that all study data is destroyed using contemporary data/sample

destruction methods as indicated in Appendix 8 of the DCM. The only exception to Appendix 8 is that the "Informed Consent" fields in REDCap will be completed in full.

- Death

Should the participant die during their study enrolment period, the RC will:

1. Document the time of cause of death in the electronic CRF
2. Inform the coordinating centre contact point
3. Include this information in annual HREC reports

9 3- and 6- Month Assessment Booking Process

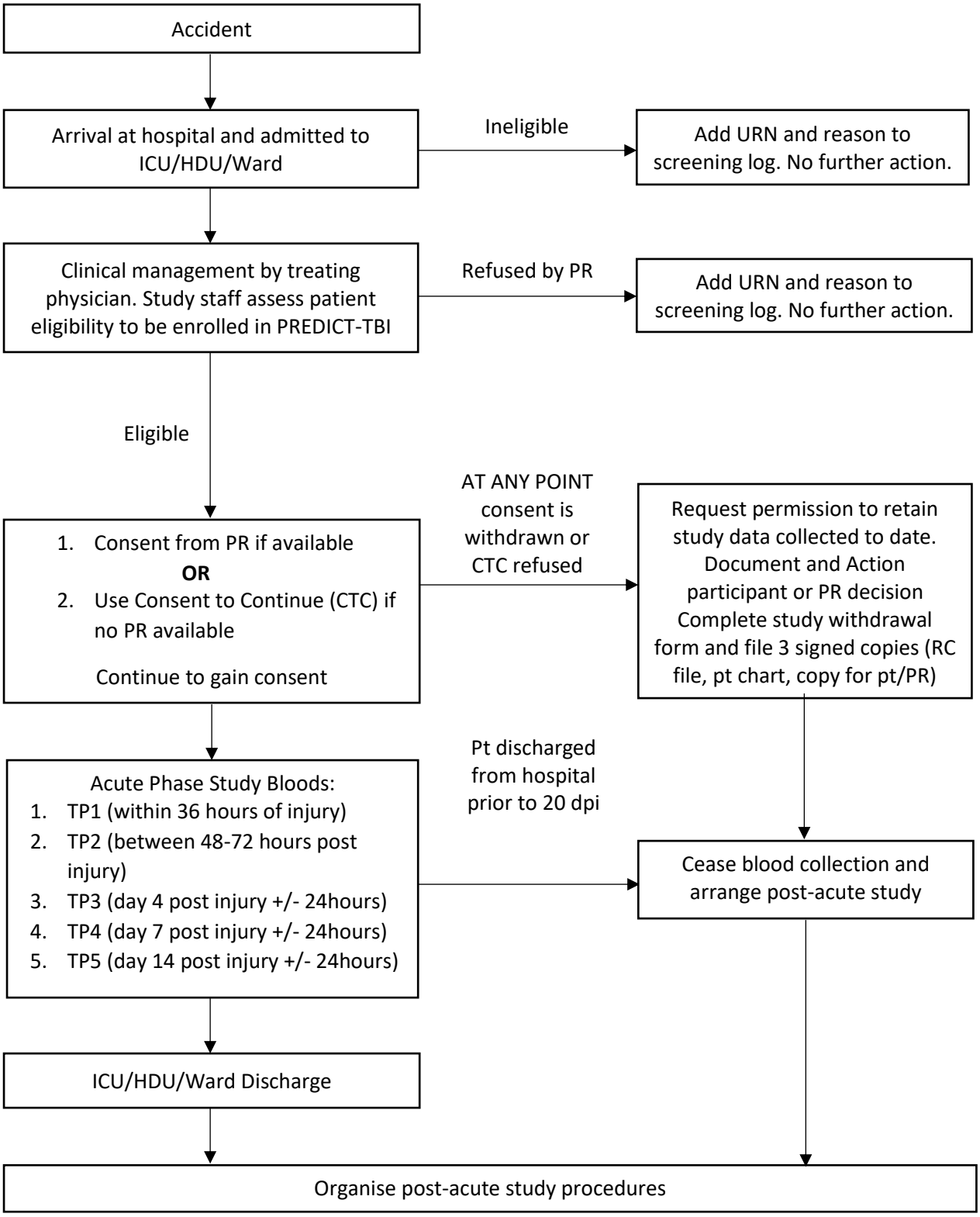
The Research Coordinator will contact participants to arrange their 3- and 6- month time-point assessments. Refer to Appendix E for details of the booking process and the responsibilities of the Research Coordinator and the Project Manager.

A travel Form (See Appendix F) will need to be completed by the Research Coordinator and sent to the Project Manager according to Appendix E.

Participants will be reimbursed for their travel expenses according to page 3 of the PREDICT-TBI PICF: "If the person lives outside the greater area of their hospital site, the study will pay for their travel, accommodation and meals. If they live within the greater area of their hospital site, the study will pay $100 for costs such as parking, petrol and/or meals".

For participants to receive reimbursement, the Research Coordinator will complete the "Research Participation Fee" form (See Appendix G) with the participant or carer, upload it into the site OneDrive folder and email the Project Manager informing them that the form is ready to be submitted to UQ Finance. UQ Finance will then process the reimbursement into the nominated bank account.

10 Appendix A. Patient Journey



11 Appendix B. Biospecimen Collection (For PAH Site Only)

Due to variations in hospital laboratory processing facilities, **samples collected at PAH must be transferred to Qld Pathology at RBWH** for processing and storage. Once drawn, PAH samples will be sent to Qld Pathology Laboratory at PAH who will then arrange to transfer them to RBWH Qld Pathology Laboratory.

Samples collected at the PAH will be sent to RBWH via the routine courier at 4°C. Below is the courier schedule for departure and arrival times; there would need to be enough time for the samples to be received in the lab at PAH and prepared for shipment to RBWH which would include sample receipt, registration, distribution to sendaways department, prepared for shipment to RBWH, including accommodating busy workload. A last blood collection of 2 pm would be recommended.

PAH Depart	RBWH Arrive
8:30	9:00
8:45	9:35
9:45	10:05
11:55	12:15
13:40	13:55
15:50	16:15

Queensland Government

Consent Information - Patient Copy
Magnetic Resonance Imaging

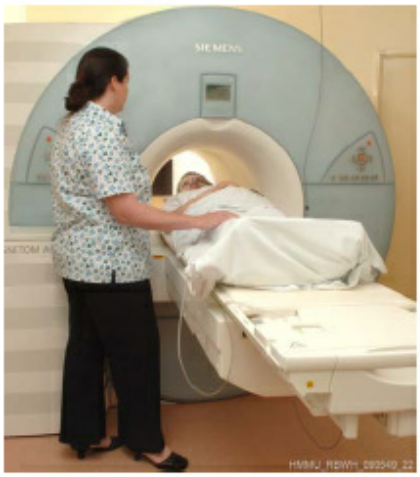
1. What is MRI?

Magnetic Resonance Imaging (MRI) is an advanced imaging method that uses a strong magnetic field, radio waves and a computer to produce pictures of the body. MRI does not use x-rays.

MRI pictures are very detailed. They can show both bones and soft tissues in the body.

MRI Safety

- *No one* is permitted into the scanning room until they have answered a series of safety questions and removed all metal objects from your body. (eg jewellery, eyeglasses and mobile phones).
- Because of the strong magnetic field there will be some patients who cannot undergo an MRI. These are patients who have metallic implants. These include but are not limited to: heart pacemakers, aneurysm clips in the brain, and foreign bodies such as metal shavings in the eyes.
- It is vital that you answer the safety questions as correctly as possible. You should discuss any internal implants (of any kind) that you may have with MRI staff to clarify any possible risks.



2. Will there be any discomfort, is any anaesthetic needed?

An MRI Scan is a painless procedure, no anaesthetic is required.

Some people find that being inside the MRI machine makes them feel uncomfortable due to the confined space of the tunnel. This is known as 'claustrophobia'. If this occurs, let the staff know as there are many different ways they can help you.

Rarely, medication *may* be required to help you complete the scan. If you require medication for the scan please check the procedure with MRI staff.

3. Preparation for the procedure

The medical imaging department will give you instructions on how to prepare for your procedure.

- Please tell the staff if you are or suspect you might be pregnant or are breastfeeding.

4. During the procedure

You will not feel anything during the scan. The radio waves used to take your pictures are *very* noisy; you may hear thumping, and knocking sounds. You will be provided with headphones or earplugs to protect your ears from the noise.

MRI staff will not be in the room with you during the scan but they will be able to see you and talk to you between the scans via an intercom. You will be given a call button to use if you need help.

The MRI scan will take between 15 and 90 minutes. It is extremely important that you keep completely still during the scan. Any movement can blur the pictures.

Depending on the area being scanned, you may be given MRI Contrast.

A fine needle (IV cannula) will be put into a vein in your arm, to inject the MRI Contrast.

For more information on MRI Contrast and the risks involved in its use, please read the **MRI Contrast Patient Information Sheet** *(if you do not have this information sheet please ask for one).*

5. After the procedure

The IV cannula will be removed (if inserted).

There are no known side effects or after effects of having a MRI.

6. What are the risks of this specific procedure?

The risks and complications with this procedure can include but are not limited to the following.

Common risks and complications include:

- Minor pain, bruising and/or infection from the IV cannula. This may require treatment with antibiotics.

Less common risks and complications include:

- No known less common risks.

Rare risks and complications include:

- Death as a result of this procedure is *very* rare.

Notes to talk to my doctor/ Health practitioner about:

_____

_____

_____

03/2011 - v2.00

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Queensland Government

Consent Information - Patient Copy
MRI Contrast

1. What is a MRI contrast?

The medical imaging MRI procedure your doctor has asked you to have may use MRI Contrast. MRI Contrast is a colourless liquid that is injected into your blood stream. MRI Contrast is not a dye. It does not stain the inside of your body. It is used during MRI medical imaging procedures to allow your organs to be seen more clearly. Your doctor needs to use MRI Contrast to be able to get all the information needed to assist with your diagnosis.

This information sheet must be read together with the information sheet of the procedure you are booked for *(if you do not have this information sheet please ask for one)*.

2. During the procedure

When the MRI Contrast is injected you should not feel any different.

3. After the procedure

MRI Contrast does not affect your ability to carry out normal activities; you should be able to continue with your day as normal.

4. Precautions

MRI Contrast is not suitable for some people; you will be asked a series of questions before it is given to you. Your answers allow staff to identify any risk factors that you may have.

- Please tell the staff if you are or suspect you might be pregnant or are breastfeeding.

Kidney function:

- MRI Contrast is removed from your blood by your kidneys through your urine. It is easily removed from the body of people who have normal kidney function.
- People whose kidneys are poorly functioning (known as 'Renal Failure') cannot remove MRI Contrast from their body. This may lead to a very rare disorder called Nephrogenic Systemic Fibrosis (NSF).
- NSF is a condition that results in scarring or thickening of the skin and tissues throughout the body. This scarring can lead to a tightening of muscle, tendons, ligaments, or skin that prevents normal movement and function. This condition is severely disabling and may result in death.
- You may be asked to have a simple blood test to find out the level of their kidney function.

5. What are the risks of MRI Contrast?

The risks and complications with MRI Contrast can include but are not limited to the following.

Common risks and complications include:

- No know common risks.

Less common risks and complications include:

- Injected Contrast may leak outside of the blood vessel, under the skin and into the tissue. This may require treatment. In very rare cases, further surgery could be required if the skin breaks down.
- The injection may not be possible due to medical and/or technical reasons.

Rare risks and complications include:

- Allergic reactions occur within the first hour with most happening in the first 5 minutes.
- The reactions vary from:
- *Mild* – headache, brief nausea, dizziness, hives, rash and itching.
- *Moderate* – wide spread hives, headaches, facial swelling, vomiting, shortness of breath.
- *Severe* – Severe reactions are rare but include: life-threatening heart palpitations, very low blood pressure, throat swelling, fits and/or cardiac arrest.
- Nephrogenic Systemic Fibrosis (NSF) for severe renal impaired patients only.
- Death as a result of MRI contrast is very rare.

6. What are the safety issues when you leave the hospital?

Go to your nearest Emergency Department or GP if you become unwell.

Notes to talk to my doctor about:

03/2011 - v2.00

Page 1 of 1

13 Appendix D. MRI Report Letter to GP

PREDICT-TBI

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA
CREATE CHANGE

Date: March 23, 2022

Sender Name:
Address:
City:
State and postcode:

Recipient Name:
Address:
City:
State and postcode:

Subject: PREDICT-TBI MRI report

Dear Dr XXXXXXXXXX

Please find attached an MRI Report for one of your patients, Mr/Mrs/Ms XXXXX XXXXXX. This report was generated as part of Mr/Mrs/Ms XXXXXX's participation in the Prediction and Diagnosis using Imaging and Clinical Biomarkers Trial in Traumatic Brain Injury (PREDICT-TBI) research study. This study has been approved by the Royal Brisbane and Women's Hospital, Human Research Ethics Committee. The study involves patients with moderate to severe traumatic brain injury and collects clinical data, biomarkers and advanced MRI imaging with the aim of improving outcome prediction in TBI. The report enclosed is the report generated by a radiologist reporting the 'conventional' MRI sequences.

Mr/Mrs/Ms XXXXXX requested this report be sent to you as it may be useful for you in the continuing care of your patient. You agree, however, that the PREDICT study investigators do not accept any liability for any clinical decisions made as a result of this report.

If you have any questions or concerns regarding the report, please contact XXXXXXXXX on XXXXXXXX to discuss these findings.

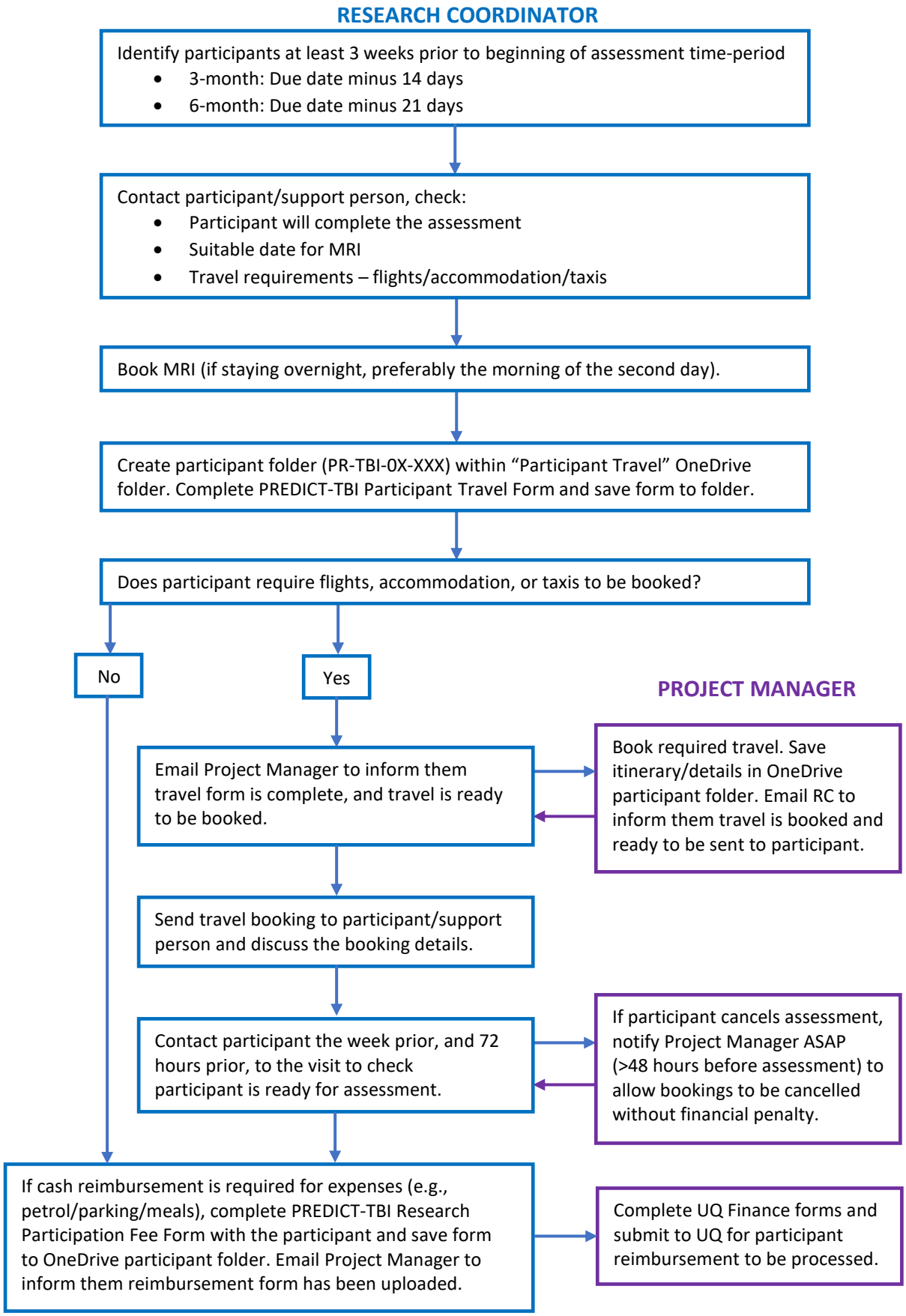
Yours Sincerely

(Insert signature)

(Insert name)

PREDICT-TBI MRI Report Letter to GP_V1.0_24 March 2022

14 Appendix E. 3- and 6- Month Assessment Booking Process



15 Appendix F. Participant Travel Form

Study ID: PR-TBI-0 __ - __ __ __

Assessment time-point: ☐ 3 months ☐ 6 months

The below details are required for reimbursement through UQ Finance and/or travel bookings.

Participant's name: _____

Contact details:

- Address: _____
- Phone: _____
- Email: _____

Support person:

Name: _____

Relationship to participant: _____

Current mobility status of the participant:

☐ Able to walk short distances unaided

☐ Able to walk short distances with walking-stick or frame

☐ Uses a wheelchair

MRI details:

MRI due date: _____

MRI booked: Date: _____ Time: _____

*Please note: MRI date and time must be booked prior to sending form to Project Manager

Flat rate of $100 required:

☐ Yes (If driving <150 kms)

☐ No (If travelling >150 kms and/or a taxi voucher is required, please complete next page with additional information)

Fuel calculation for driving >150 kms required:

☐ Yes ☐ No

If yes, driving from _____ to _____

Flights Required:

☐ Yes ☐ No

If yes:
Departure Airport: _____

Assistance required at airport (e.g., wheelchair to gate/plane entrance/seat):

_____

_____

Overnight accommodation required:

☐ Yes ☐ No

If yes:
Number of occupants: _____

Type of room required (e.g., Queen bed, 2 single beds etc): _____

Ambulant or wheelchair room: _____

Taxi trips required (Please note, only taxi trips that have been booked will be available for use):

☐ Yes ☐ No

If yes:

☐ Airport to Accommodation

☐ Accommodation to hospital

☐ Hospital to Airport

Please state any other trips required for voucher:

_____

Any relevant information related to the participant's injury that will affect travel requirements:

_____

_____

16 Appendix G. Research Participation Fee Form

Research Participation Fee, for contribution to PREDICT-TBI Study ID: PR-TBI-0X-XXX	
Participant's Full name:	
Financial Institution Name:	
BSB Number	__ __ __ - __ __ __
Bank Account Number	
I declare that the banking information provided above is accurate and correct, to receive the fee of $XX associated with my participation (as a human subject) in the above study. **Declaration, signature: _____Date: _____**	
Research Coordinator **Name**: _____ **Signature**: _____ **Date**: _____	

The information contained in this form will be managed with strict confidentiality and stored on the secure UQ Research Data Management system.

PREDICT-TBI Research Participation Fee_V3.0_24 March 2022