August 18 2021

Cover letter

To whom it may concern, please find attached the protocol titled '**Protocol of a pragmatic randomised controlled trial of intramuscular haloperidol plus promethazine plus chlorpromazine versus intramuscular haloperidol plus promethazine plus chlorpromazine in the Lebanese psychiatric setting**' dated August 21, 2018 in PDF/A format.

Kind regards,

Protocol of a pragmatic randomised controlled trial of intramuscular haloperidol plus promethazine plus chlorpromazine versus intramuscular haloperidol plus promethazine plus chlorpromazine in the Lebanese psychiatric setting.

5.1 Overview

Chapter IV was a systematic overview of relevant trials and it concluded with showing the emergency treatment used in Lebanon (See Chapter III) is unique to Lebanese medical practice. This chapter will focus on the trial protocol building on chapter III (treatment in Lebanese practice) and chapter IV (Systematic overview of relevant trials pertaining to rapid tranquilisation).

This is a research protocol of the clinical trial that is to be conducted in the Lebanese psychiatry setting. It describes how the clinical trial will be conducted (I.e. objectives, statistical considerations, design, methodology and organisation) and ensures the ethical integrity of the trial subjects and data acquisition have been considered. Moreover, the protocol (now registered and published) serves as an indicator that the trialists will conduct the trial in accordance to what is presented in the trial protocol. Should the trial stray in any of

its aims (i.e. result objectives), the trialist is obliged to explain why changes were implemented.

5.2 Introduction

Aggressive and violence behaviour is a common behaviour seen in emergency psychiatric presentations with a prevalence of 3-10% (Tardiff & Koenigsberg, 1985). This aggression is due to a range of psychiatric disorders such as schizophrenia, bipolar disorder, substance use, and personality disorders as well as organic problems such as dementia although they are less frequent with the latter (Kaplan & Sadock, 1998). Guidelines recommend aggressive patients to be 'verbally tranquilised' in order for the attending physician to accurately and safely perform a diagnostic history and physical examination (The expert consensus guideline series, 1999). Since aggressive patients make this process difficult and potentially impossible, doctors and nurses face a dilemma and are required to work with limited evidence. Since the psychiatric team has a responsibility of ensuring the safety of everyone, rapid and safe tranquilisation becomes unavoidable. Medication and physical restraints are the available options when planning to calm and tranquilise an agitated patient. Medication can be given orally, intravenously (IV) or intramuscularly (IM). Oral and IV medications are usually not

possible when the patient is lashing out aggressively (Yildiz, Sachs, & Turgay, 2003). Depending on where in the world the management is happening, physical restraints may include straitjackets (Colaizzi, 2016), use of seclusion rooms (Crespi, 1990) or medical restraints binding the patient safely to a bed using two or four points (Fisher, 1994; Saks, 1986). Physical restraining by staff is commonly employed.

All options have advantages and disadvantages. For example, IV medication may work faster when tranquilising an agitated patient but may also lead to cardiac and respiratory problems – not to mention extreme difficulties implementing IV needles with an aggressive patient (Atakan & Davies, 1997). IM medications are easier to administer making them more efficient in terms of implementation. However, the time to onset of calming or sedation is longer and unpredictable compared to IV (Kaplan & Sadock, 1998). Physical restraints have the advantage of preventing patients from physically assaulting staff as well as causing self-injury. They also have the advantage of being more efficient when used in combination of drugs being delivered via IV or IM (Currier & Trenton, 2002). However, the disadvantages of restraints include out of date practice (depending on country) and time taken for patient to achieve a state of calm is profound when compared to pharmacological interventions (Miles & Irvine,

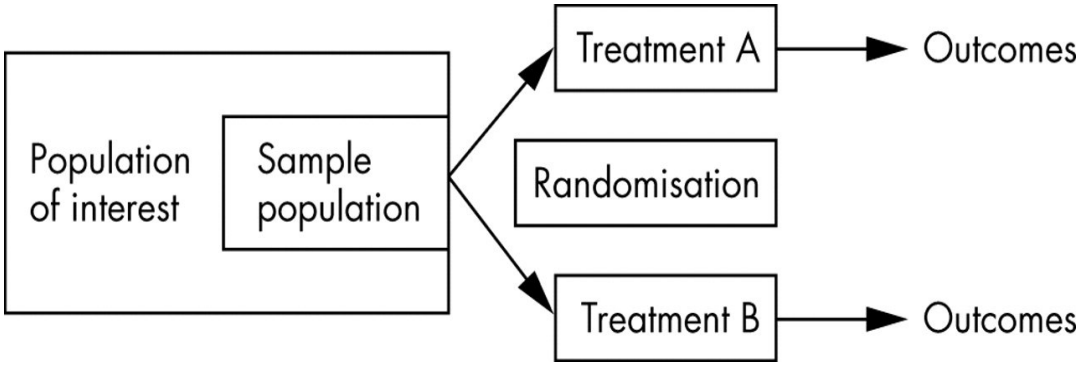
1992). It is imperative to find an evidence-base for a management scheme that is humane, socially acceptable and suited to tranquilise/calm aggressive patients safely and rapidly. This will help ensure the safety of both patients and the workers involved. TREC-Lebanon is a randomised, controlled, pragmatic and open study. Primary measure of outcome is tranquilisation at 20 minutes but effects on other measures of morbidity will also be assessed. TREC-Lebanon will involve the collaboration of many health care professionals – clinicians and psychiatric nurses in wards whereby the trial is taking place. Because the design of the trial does not substantially complicate clinical management, and in several aspects simplifies it, the study has the potential to be large and to evaluate treatments used in everyday practice.

5.2.1 What is a randomised controlled trial?

A randomised controlled trial is a type of study in which a number of similar people are randomly assigned to two (or more) groups in order to test a specific drug, treatment or intervention The experimental group receives the intervention being studied while the control group receives a placebo, no intervention or an alternate intervention. Outcomes are measured at specific times and the differences are examined statistically. This method is used to reduce bias (National Institute of Clinical Excellence, 2005). Figure 5.1 shown below

is a classic example of the basic structure of a randomised controlled trial (Akobeng, 2005).

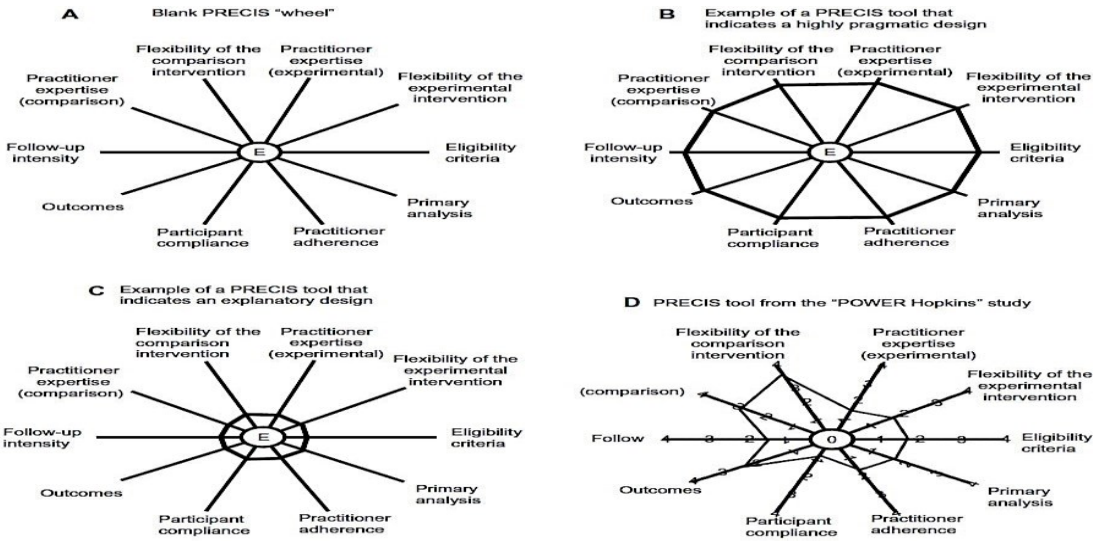
Figure 0.1: The basic structure of a randomised controlled trial



5.2.3 What is a pragmatic randomised trial?

The term explanatory is used to describe trials that aim to evaluate the efficacy of an intervention in a well-defined and controlled setting, Pragmatic or 'real-world', however, is used for trials designed to test the efficacy of the intervention in routine clinical practice (Patsopoulos, 2011). For example, a trial intended to inform a research decision regarding the benefit of a new drug is more likely to be explanatory reflecting ideal conditions while those for a later trial of the same drug intended to inform practical decisions by clinicians are more likely to be pragmatic as they reflect the usual conditions (Thorpe et al., 2009). The PRECIS instrument has been developed to guide trial design at the planning stage but also serves in other applications such as peer reviews attained in study reports (Winter & Colditz, 2014).

Figure 0.2: PRECIS tool



5.2.4

Rapid tranquillisation

Rapid tranquillisation (RT) is not considered a 'treatment' for a persons' mental health condition, but a short-term management technique for severely agitated and/ or aggressive behaviour in people experiencing psychotic distress. Due to its restrictive nature, RT should only be used as last resort when all other attempts to calm a situation via prevention (being environmentally aware and ensuring that adequate numbers of staff are present on ward) and de-escalation (talking to and verbally trying to calm the person) has failed. These interventions should always be used in a way that respects human rights, and should never be used to manage patients as a substitute for adequate staffing (Department of Health, 2015).

5.2.5 Lebanese National Guidelines

There are no Lebanese national guidelines pertaining to rapid tranquilization. As illustrated by Chapter IV, evidence from trials regarding the emergency intervention favoured in Lebanon (Chapter III – HPC) does not exist, although there is a good evidence base for the HP combination that is also used in Beirut. This affords opportunity to compare these two management plans, in real world circumstances, within a pragmatic randomised trial. This will be first of its kind comparing these two approaches, but also the first of its kind in psychiatry in Lebanon.

5.2.6 TREC

TREC-Lebanon derived its name from the first Brazilian TREC-Rio study. TREC, in Portuguese, was an abbreviation for 'Tranquilização Rápida-Ensaio Clínico' [Rapid Tranquilisation Clinical Trial]. TREC-Lebanon, similar to TREC-Rio and TREC-India, will be investigating rapid tranquilisation within a clinical trial for treatment of agitated people in emergency psychiatric wards - in this case in Deir Salib – Lebanon's largest and only public psychiatric hospital.

5.3 Methods

5.3.1 Eligibility

TREC-Lebanon is a pragmatic trial with wide, easily applied eligibility criteria that have been drawn up by the researcher (JD) working with partners in the Psychiatric Hospital of the Cross, Beirut.

a. Inclusion criteria

Patient will be eligible if (1) requiring emergency acute intramuscular sedation because of disturbed and dangerous behaviour and (2) if the clinician is uncertain of the benefits between haloperidol plus promethazine vs. haloperidol plus promethazine plus chlorpromazine.

1. Gender – both male and female
2. Age (18-64)

b. Exclusion criteria

1. If the clinician KNOWS one treatment has benefit over another for a particular person
2. If the clinician is aware of a contra-indication of one of the treatments
3. If there is an Advanced Directive expressing a wish for one or other, or another treatment in the emergency setting

4. If the clinician does not want to undertake for both personal and professional reasons
5. If the participant is known to be allergic to one or more of the interventions
6. Already randomized
7. Already sedated
8. Accompanying person (Friend/Family/Police Officer) refuses patient trial entry.

Table 0.1: TREC- Lebanon plan

Eligible if	*1. Patient is needing acute intramuscular sedation because of disturbed and dangerous behaviour* *2. Clinician is uncertain about the benefits and risks of haloperidol plus promethazine versus HPC*
Exclude if	1. The Clinician believes that one treatment represents an additional risk for the patient
Trial Entry	2. Treatment is allocated using opening of consecutive TREC envelopes stored in the emergency drug cupboard. The envelope contains: 1. The treatment paper slip indicating intervention to use 2. TREC forms to be filled out by the attending doctor/resident 3. TREC stickers for the patient's notes
Treatment	4. Either: 5. Haloperidol (2x5mg ampules) + promethazine (1x50mg ampules) Or: 6. HPC (Haloperidol 5 mg, Promethazine 50 mg and Chlorpromazine 100 mg ampule) 7. One or other indicated on paper slip in the TREC envelopes 8. All doses are at the discretion of the doctor
Follow up	1. All people for whom an envelope is opened will be followed up by the TREC study co-ordinators 2. Data will be extracted from the notes on clinical state, hospital status, sedations, use of additional medications, and adverse reactions

5.3.2 Interventions

Placebo controlled studies in this area are difficult to justify on ethical grounds (see section on ethics in chapter **Error! Reference source not found.**) although the UK National

guideline (National Institute of Clinical Excellence, 2005) does use evidence from such studies (See here). TREC-Lebanon, however, will evaluate the existing care in the health services of Lebanon (Chapter VI) and this care involves the use of medication that is considered – and most likely is - both safe and effective. Currently, this protocol includes a comparison of an intramuscular haloperidol-promethazine mix (HP) with an intramuscular haloperidol-promethazine-chlorpromazine mix (HPC).

The triple mix (HPC) is an obvious choice for TREC-Lebanon. It is perceived as effective, safe, and with adverse effects that are readily recognised by both medical and nursing staff in their routine care (See Chapter III). It is easy to administer by intra-muscular injection but has never been evaluated within a randomised control trial. As seen in Chapter III, the HP mix is also used in Beirut, albeit less frequently. Haloperidol, promethazine and chlorpromazine are on the WHO's Model List of Essential Drugs (See here) (World Health Organization, 2015).

a. Chlorpromazine

Chlorpromazine is one of the three listed drugs for treating psychotic disorders in the World Health Organization's Essential Drug List (World Health Organization, 2013) (See

here). It is used across the globe for the 1% of people who suffer from this illness (de Haan & Liu, 2009). Chlorpromazine has a number of adverse effects, including a range of movement disorders (extrapyramidal symptoms) and anticholinergic and antihistaminic effects (Abidi & Bhaskara, 2003). Chlorpromazine is known to be the most epileptogenic of the conventional antipsychotics causing seizures ranging from 1-4% depending on dosages (Hedges, Jeppson, & Whitehead, 2003).

b. Haloperidol

Haloperidol is an effective antipsychotic also listed in the World Health Organization's Essential Drug List (World Health Organization, 2013)A key adverse effect caused by haloperidol are acute dystonias which are involuntary contractions of muscles all over the body such as the neck, face, pelvis, extremities, etc. and occur in 40% of all patients under haloperidol treatment (Kurz, Hummer, Oberbauer, & Fleischhacker, 1995b). They are not life threatening but can be distressing and frightening to the patient. Acute dystonias are successfully and swiftly treated with use of anticholinergic medication such as promethazine or procyclidine (Adams, Bergman, Irving, & Lawrie, 2013). However, these events are highly unpleasant and must further erode trust in the services.

c. Promethazine

Promethazine hydrochloride is a first-generation H1 receptor antagonist, antihistamine, and antiemetic medication that can also have strong sedative effects ranging from mild to heavy and is used in relieving extrapyramidal symptoms caused by antipsychotic medications (Cantisani et al., 2013). Anticholinergic manifestations such as dry mouth, mydriasis, and blurred vision are usually present. Overdosage may also present with various cardiorespiratory symptoms such as respiratory depression, tachycardia, hypertension or hypotension, and extrasystoles (Lazarou, Pomeranz, & Corey, 1998).

d. The combinations

It is well known that combining drugs can change - increase or decrease - the incidence of the known adverse effects (Lemmens, Brecher, & van Raelen, 1999) or result in novel effects unheard of with each drug on its own (Rummel-Kluge et al., 2010). The HP combination is, however, widely used and trusted. The addition of the promethazine to haloperidol may increase sedation, but decrease the acute dystonia so often seen with haloperidol alone. The latter was so common in the haloperidol alone arm of the TREC-Rio-II trial (Haloperidol vs. haloperidol + promethazine) and rare in the

second arm of that study that the trial was halted early by the Trial Steering Group (Huf, Coutinho, & Adams, 2007). It was felt that the combination treatment had considerable advantages over the haloperidol alone arm and that it was unethical to continue randomising to such a toxic treatment. (This latter treatment continues to be commonly employed within UK practice and can be seen in the 2017-2018 Prescribing Observatory For Mental Health: Available to download here) (Prescribing Observatory for Mental Health (POMH-UK), 2018).

The combination of haloperidol, promethazine and chlorpromazine (HPC) seems to be less commonly used than the combination of haloperidol and promethazine. However, HPC is still used in everyday practice at least Brazil and Lebanon (Dib et al., 2018a; Huf, Coutinho, & Adams, 2002). Whether the further addition of another drug (chlorpromazine) is a benefit or causes difficulties will, partly, be illustrated by the results of this study but no literature has been found to suggest that there are novel or even extreme adverse effects of this triple combination. Chapter III's survey of Lebanon has shown that this intervention has been commonly used in psychiatric practice – probably for many years - with success in attaining rapid tranquilisation as well as causing very low incidence of adverse effects.

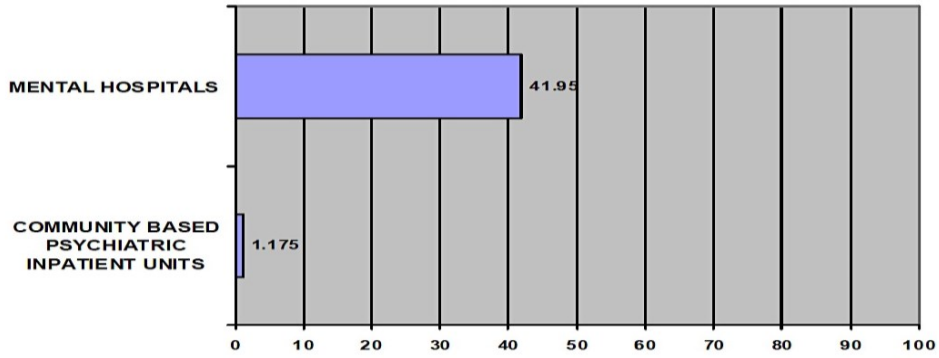
5.3.3 Setting

The prevalence of serious mental illness across the world is 1-2%. 80% of people live in low or middle income countries where typical antipsychotics such as haloperidol and chlorpromazine and/or benzodiazepines are readily available. Lebanon ranks as a low to middle income country (El Laithy, Abu-Ismail, & Hamdan, 2008). And, indeed, the 'typical' antipsychotics plus benzodiazepines are used (Chapter III).

There are three mental hospitals and five psychiatric units within general hospitals in Lebanon. There are a total of 43 psychiatric beds per 10,000 population (figure includes both psychiatric beds in general hospitals and mental hospitals). Two psychiatrists per 100,000 populations can be found in the general Lebanese population. Lebanon depends mainly on the private sector for the provision of the health services. The Ministry of Health has contracts with several private sector providers so patients can receive 'free' treatment. There are no disability benefits for persons with mental disorders and no disability funding for mental health (Berger, 2007). There are also no existing data on people who are treated in mental health hospitals, general hospital and community based psychiatric units. At best, by combining data from below on Lebanon's economic social status and data from the WHO-AIMS report on Mental Health in Lebanon (World Health

Organization, 2010), it can be assumed that since the majority of patients are treated in mental hospitals compared to community based psychiatric inpatient units (See Figure 5.3) and that the majority of the population require services from the Ministry of Health as they cannot afford private insurance, the majority of people seeking treatment for mental health would choose public psychiatric hospitals over private (Berger, 2007).

Figure 0.3: Patients treated in mental health facilities (rate per 100.000 population)



5.3.4 Size and statistical considerations

Two main factors determine the number of people who should be recruited in a randomized trial in order for the trial to provide clear answers. They are the frequency of the investigated event and the size of the effect of treatment. It is important to avoid results that are erroneous. The probability of producing so called 'false-positive' results (Type I error – a) and 'false negative' findings (Type II error – B) is minimised by having adequate sample size. The aim of TREC-Lebanon is

to investigate whether people do 'better' if they get HPC or HP and 'better' – the primary outcome - is the proportion of patients' calm/tranquil at 20 minutes.

In such a stressful situation, even a small advantage for an intervention could represent a worthwhile benefit and so, TREC-Lebanon has been planned so that even a 15% difference in the proportion of tranquilised patients within the 20 minutes could be detected. Realistically, and calculated from work in Chapter III and the time constraints of this PhD, TREC-Lebanon expects to involve a minimum of 90 patients across at least in a 3 month period.

Table 0.2: Sample size needed to detect an absolute difference

HP (% tranquilised)	HPC (% tranquilised)	*N*
5	20	152
10	25	200
15	30	242
20	35	276
25	40	304
30	45	326
35	50	340

As seen above sample size needed to detect an absolute difference of 15% in the proportion of tranquilised patients with alpha being 5% is greater than what TREC-Lebanon is projected to accrue. Therefore, TREC-Lebanon may well be underpowered to detect real effects and will not hold the same strength as TREC-Rio and TREC-India. However, the difference

between the two management strategies under test could be greater than 15%. Also, TREC-Lebanon is the first of its kind, it will serve as a vanguard for such studies in the Middle-East and properly test feasibility, as well as being a pilot for trials to come.

5.3.5 Ethical and legal considerations

The Helsinki Declaration (World Medical Association, 2013), the European Directive on Clinical Trials (European Parliament, 2002) and the Nuffield Council documents on bioethics (Nuffield Council, 2000) state that trials in non-consenting patients are permitted on two conditions: i. no other context exists in which to answer the question; and ii. All trial participants get clear therapeutic benefit from whichever arm they are randomised to.

The mental health system benefits from different acts and legislations in different areas of mental health (Berger, 2007), namely:

1. Lebanese Act no. 72-9/9/1984 Welfare Act and Protection and Treatment of Mentally Ill Patients.
2. Lebanese Act no. 673-16/3/1998 Narcotic Drugs and Psychotropic Substances and Precursors.
3. Lebanese Act no. 220-29/5/2000 Rights of Mentally Handicapped in Lebanon.

4. Lebanese Act no 574-11/2/2004 Patients' Rights and Informed Consent.

Aggressive patients in a situation of psychiatric emergency are not able to give consent for their participation in a study. Drugs are usually given against the will of the patient. So, in the same way that doctors are responsible for the choice of a treatment in routine care, they take responsibility for the recruitment of a patient into the study as well as seeking consent. However, TREC-Lebanon will not involve administering an inactive compound to those who clearly need sedation/tranquillisation. Both treatments can calm the patient and there is no 'experimental' intervention. What is still uncertain is the speed for the onset of action, the duration of the effects and the different kinds of adverse reactions. TREC-Lebanon will answer clinical questions to help the care of these people be more informed. TREC-Lebanon will also produce widely applicable findings, so that the treatment of people beyond Lebanon should also be safer.

A patient/carer information leaflet about TREC-Lebanon is available for all for whom a TREC-Lebanon envelope is opened. Carers will always be free to decide that their relative should not be entered. Not being involved in TREC-Lebanon will not affect the person's standard of care. An information sheet is

provided detailing the aim and purpose of the study (See 5.8 Appendix 1. TREC- Lebanon information for relatives).

5.3.6 Randomisation

Randomisation allows the distribution of the treatments in a way that is not a function of a clinical decision, but of pure chance. Clive Adams will undertake randomisation in the United Kingdom. Microsoft Excel 'RAND' function will be used to choose even numbered block sizes less than ten. Again using this function, the order of use of these block sizes will be randomised. Which drug regimen was represented by which number within the block was then selected, again at random. Tables of TREC-Envelopes numbered by contents will be constructed and will be supplied to a Lebanese colleague (Souheil Hallit). The tables will list the contents of the envelopes in groups of ten, not disclosing the block sizes used. The Lebanese colleague, always working independently of the TREC-Lebanon team, will ensure that the correct labels are in the TREC-envelopes before they are sealed. Concealment of allocation will be ensured by not disclosing the randomly varied block sizes to the colleagues packing the envelopes, the supply of tables to those colleagues that gives no suggestion that blocks are even being employed, the independence of those filling the envelopes from the other researchers or the

clinicians, and the identical nature of the sealed, fully opaque envelopes.

These easy-to-use envelopes will be paper based, identical and consecutively numbered. The final check to ensure that nothing has gone wrong with the randomisation will be by the principal investigator (JD) filling in a form for each block of ten opened envelopes.

5.3.7 TREC-Lebanon

Because the TREC-Lebanon study evaluates care in the emergency situation, it is imperative that the doctors and nurses know which intervention is being given. The study is blind only up until the time that the TREC-Lebanon trial envelope is opened. Therefore, it is crucial that the evaluation of the severity of a person's disturbance and the first impression on the possible cause for the disturbed behaviour are recorded *before* the envelope is opened. Once the envelope is opened, doctors and nurses will have knowledge of the drug to be used. It is perfectly feasible that the knowledge that one drug has been given will influence the care beyond the actual effects of the medication. Keeping the study open is not only practical in the emergency situation, but also desirable as the evaluation of care being undertaken is as near real-world circumstances as is possible.

5.3.8 Protocol registration

The objective of registering trial protocols is to establish a comprehensive register that would make all protocol of trials publicly available (Dickersin & Rennie, 2003).

Reference number supplied by the chairman of the committee of The Psychiatric Hospital of the Cross Lebanon: HPC 001/2018.

Reference number supplied by the ethics board of the University of Nottingham: 271.

5.4 Procedures

All trial materials, and guidelines for their use, are to be provided in the TREC-Lebanon folder supplied by the co-ordinating centre. What follows is a brief summary of all of trial procedures.

5.4.1 Fitting into everyday practice

The TREC-Lebanon trial is designed to not interfere with routine care. The process of randomisation is very similar to the normal procedure at the beginning of treatment and the eligibility criteria are simple. A paper slip indicating what intervention to use will be packed within the envelope. Data collection will be limited to the minimum necessary, and will involve little more than extraction of routine information by a

person designated to spend time on the TREC-Lebanon trial. It is not envisaged that busy doctors and nurses will be spending time filling out complicated forms.

5.4.2 In the community

Chapter III survey showed there are times when patients are brought in after having been given a sedative to calm down by their parents, friends or law officials. In this situation, as far as the clinician is concerned, he or she must still decide if the patient should be randomised if the patient is still exhibiting an agitated episode.

5.4.3 Arrival at hospital

Most people arrive at the hospital's administrative centre are registered as a patient, and then transferred into their ward. If patients are presenting with violent conduct that could potentially harm people in their vicinity, they are taken immediately to the designated ward while those who brought them to the hospital (Family, friends, police officers, etc.) fill out paperwork and present their documents to the hospital's administration. Patients that display an agitated episode requiring rapid tranquilisation are usually calm while waiting in the ward. Upon being told they cannot leave until they are feeling better, they may then display an agitation or aggression.

5.4.4 Triage to randomisation

a. Eligibility and randomisation by envelope.

Carers accompanying the disturbed person should have an opportunity to see the information leaflet (5.8 Appendix 1. TREC- Lebanon information leaflet for relatives) before randomisation.

Anonymised information on participants who are not randomised / registered will include:

- Age,
- Gender,
- Ethnicity (if applicable),

The reason not eligible for trial participation, or if they are eligible but declined.

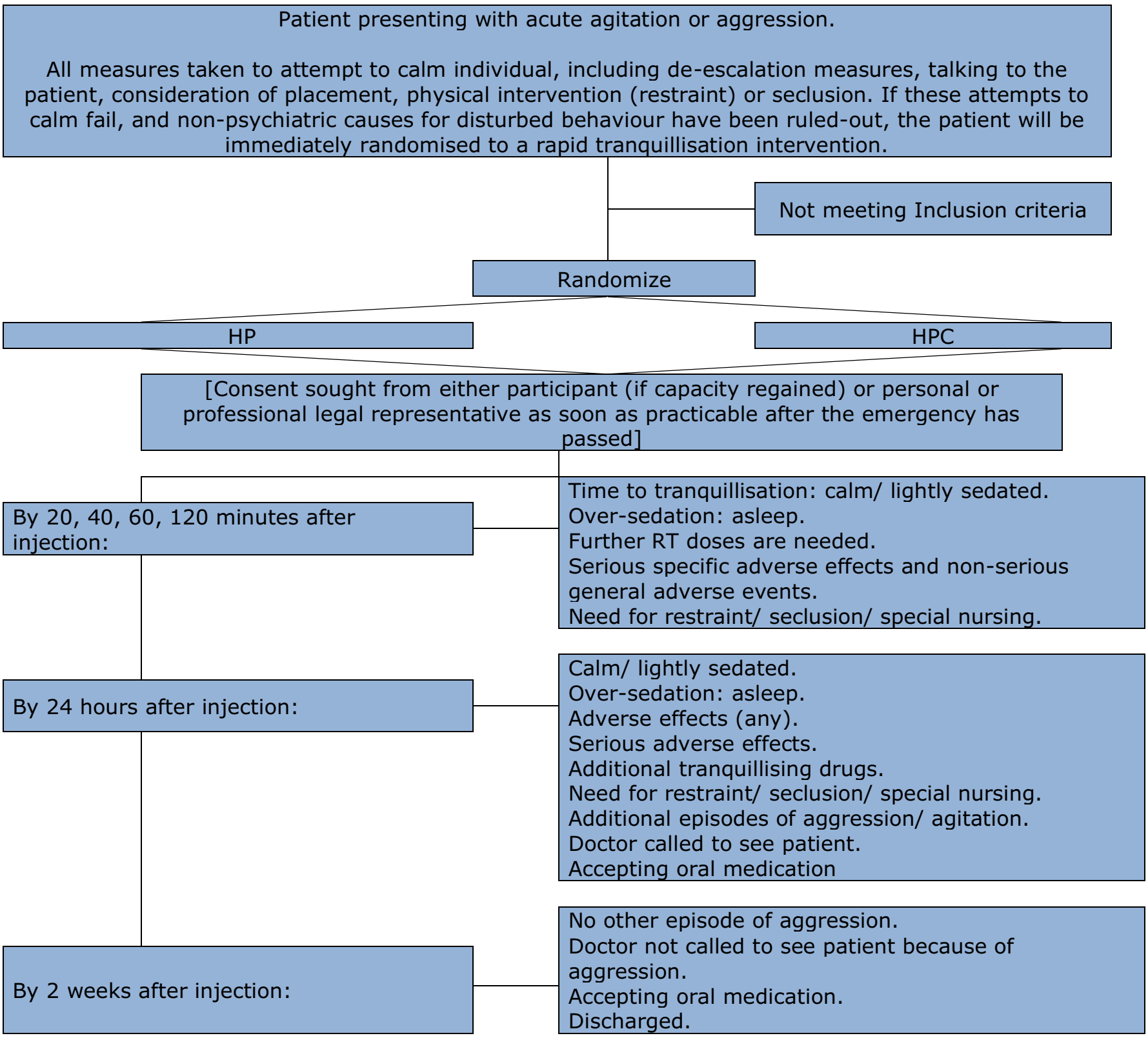
Randomisation proceeds using a local pack system. Identical sealed treatment envelopes are provided.

As soon as the person enters the study, the clinician completes the trial entry form *on the top of the next consecutive envelope* (See 5.9 Appendix 2. TREC-Envelope entry form – completed blind to treatment allocation). This must be completed *before* the treatment envelope is opened. It records brief baseline details about the person and the number of the treatment envelope. The treatment envelopes *must* be used in

order in which they are removed, the lowest number first.

Once the trial entry form has been completed the person is in the trial, even if the doctor changes his/her management and the treatment envelope is not opened.

Table 0.3: Follow up enrolment



5.4.5 Participant Eligibility Criteria

The eligibility criteria should be clear (See Eligibility above in Methods section).

5.4.6 Trial envelopes

As soon as the person has been found to be eligible, the next consecutive envelope is opened and a paper slip indicating what intervention to use is displayed. Each envelope contains:

Paper slip indicating the use of haloperidol + promethazine (HP)

1 × TREC-Lebanon follow-up form (Appendix 3, see Additional File 1)

2 × TREC-Lebanon stickers for the drug prescription form and medical notes

Or

Paper slip indicating the use of haloperidol + promethazine + chlorpromazine (HPC)

1 × TREC-Lebanon follow-up forms (Appendix 3, see Additional File 1)

2 × TREC-Lebanon stickers for the drug prescription form and medical notes

All doses used are at the discretion of the attending clinician. If the contents of a trial envelope are destroyed, or unfit for use, the person should *not* be randomised a second time and

the equivalent material should be obtained from the research director (SH) if appropriate.

In the event of continuing aggression despite the TREC-Lebanon medication, on-going emergency management would be up to the discretion of the clinicians. Another envelope *is not* opened and the doctor is free to use any standard interventions.

5.4.7 Outcome and follow-up

It is crucial that follow-up is complete and accurate for everyone entered into the study. As a pragmatic study, causing minimal interference with routine care, TREC will not employ any rating scale outcomes. It is likely that completion of scales would be inaccurate, and incomplete, validity and reliability would be in question, and clinical utility problematic. The main outcome of TREC-Lebanon is tranquillisation by 20 minutes. This primary outcome was requested by the nursing and medical staff of the hospital. By asking the relevant clinical staff to select the primary outcome for TREC-Lebanon we hoped to ensure maximum compliance with the trial protocol. Therefore, upon injection of the patient, a timer is started on the resident's phone and this rings at 20 minutes and then again at 40, 60 and 120 minutes. At each period the attending resident rates whether the person is tranquil,

asleep, has shown adverse effects or needs additional treatment (see 5.9 Appendix 2. TREC-Envelope entry form - completed blind to treatment allocation). This attending resident is not blinded. The person is considered tranquillised when they are felt to be calm and peaceful, but not asleep. They should not be agitated or restless, nor displaying threatening verbal behaviour, physical aggression against objects, self-aggression or physical aggression to other people. Blinding this rater for every participant would have added additional complexity to the study that would have made the trial unacceptable to the emergency room staff. More importantly, it would have completely changed the emphasis of TREC-Lebanon. What is being evaluated is the real-world practice of giving two different drug regimens in the psychiatric emergency setting. In the real world situation health care professionals know what treatment is being given.

In addition, nurse volunteers should they choose to participate can be an additional rater, blind to allocated treatment who will, unknown to the health professionals looking after the patient, time the period between injection and tranquillisation and / or sleep exactly. These data will be used to validate the rating of the follow up form (see 5.11 Appendix 4. Dr. Stopwatch Form). Additional data are then recorded at 24

hours and finally at two weeks (See 5.13 Appendix 6. TREC-Lebanon Main data collection form).

All additional data are to be extracted from routine notes. If the person is transferred to another hospital, the co-ordinating centre will contact every hospital to find out further details on outcome after transfer.

5.4.8 Data collection, entry and analysis

All data for TREC-Lebanon will be collated from the TREC-envelope forms and routine notes of each emergency room or ward (See 5.13 Appendix 6. TREC- Lebanon Main data collection form). These data, in compliance with the Nottingham ethics committee requests, will be protected via anonymising the personal data of trial participants. The data will be inputted onto Microsoft Access (Or a program of similar nature).

Analysis will take place within this package and SPSS. Tables for this analysis are prepared before recruitment of the first patient (See 5.14 Appendix 7. Dummy Tables). All analysis will be based on groups as randomly allocated; this will be an intention-to-treat analysis. For the principal comparisons statistical significance will be taken at a 5% level, to minimise the impact of multiple comparisons. Relative risk, risk difference and 95% confidence intervals will be estimated for

tranquillisation by 20 (Primary outcome), 40 and 60 and 120 minutes (Secondary to primary outcome). For simplicity, SPSS will primarily be used to run frequency tables. Revman will be used to calculate risk ratios and confidence intervals between interventions.

5.5 Anticipated risks

In the following subtopics I will discuss all the risk associated with the TREC-Lebanon along with how these will be assessed and mediated.

5.5.1 Ineligible people entering the study

It is possible though highly improbable that patients who do not fit the trial's entry criteria may enter the study. Those that do will not be counted as part of the trial and their notes will be disregarded. Detecting ineligible patients will be seen in the data entry form left at the director of research's office (SH) making it simple and direct to trace.

5.5.2 Staff compliance with protocol

Attending resident and nurse should monitor action of given intervention i.e. make sure given treatment has been injected properly. In the event that an agitated patient may break any of the treatment tools – mainly the syringe containing the treatment intervention or destroy the vial containing the

intervention before being placed within the syringe, another TREC envelope should *NOT* be opened. Instead, attending resident should carry on as per hospital protocol and fill out the serious event form detailing the circumstances (See Appendix 5. Serious event form). Nurses should also detail the nature of compliance, as they would normally do in their notes. In the event a patient does break the syringe or capsule, the situation is rectified with the nurse bringing the emergency treatment as detailed in the paper slip in the envelope.

5.5.3 Feasibility phase

A feasibility phase will take place before the trial commences. The feasibility phase will include a limited number of envelopes (5) with contents known to the trialists. The feasibility phase is designed to test the trial's procedure in practice in order to assess if any unforeseen circumstances arise. In the event such unforeseen circumstances do arise, the trialists will rectify and mediate in the most practical way possible. Changes will be noted by the head researcher (JD) and updated in the trial protocol.

5.5.4 Additional envelopes

Ineligible people entering the study (see above) are at risk of using trial envelopes designed for patients eligible for the trial

only. This ultimately affects the balance of both intervention samples therefore one solution is that a limited number of TREC-Lebanon envelopes will be crafted or bought for the trial beforehand and will be placed in SH's secure office to ensure the trial has a balanced sample between two groups.

5.5.5 Toxicity and serious unexpected events

After trial entry, clinical events are recorded, as usual, in the patients' notes. Complications and adverse events should be managed as usual. A serious unexpected event form (5.12 Appendix 5. Serious event form) is provided, and will be sent to the TREC-Lebanon Co-ordinator (JD) as soon it is completed. As mentioned in the eligibility criteria above, the attending doctor retains the right to withdraw the patient and the Steering Committee evaluates the overall circumstances of the event. In the event toxicity levels are more prevalent than anticipated, the Steering Committee may terminate the trial.

5.6 Trial organisation

The TREC-Lebanon Co-ordinating Group: The co-ordinating centre of the Lebanese arm is based at the Institute of Mental Health University of Nottingham United Kingdom. The Co-ordinating Group has overall responsibility for the design of the proposed trial and is responsible for all aspects of day to day trial administration. The Co-ordinating team is also

responsible for preparing reports for the steering committee. Membership: Joseph Dib, Clive E Adams, Souheil Hallit.

5.6.1 Steering Committee

The overall progress of the trial, adherence to protocol, patient safety and the consideration of new information will be monitored by a scientific and administrative Steering Committee. The membership of this committee is PS and RH.

5.6.2 Data Monitoring Committee

TREC-Lebanon will include a committee to oversee progress of the trial. Since TREC-Lebanon might take three to six months to complete, an independent data monitoring committee (DMC) will, in confidence, monitor results. This could be undertaken on a week to week or month to month basis depending on the collective agreement of all the members of the DMC. In the light of the interim data, and of any other evidence or advice they wish to seek, the DMC will inform the chair of the Steering Committee (PS) if, in their view: i. there is proof beyond reasonable doubt that for any particular group or subgroup treatment with one or other regiment is clearly indicated or contraindicated or: ii. it is evident that no clear outcome will be obtained. Proof beyond reasonable doubt may be taken as the difference of at least three standard deviations and at least one of the primary outcomes.

The DMC may communicate certain interim analysis to the SC or suggest certain protocol changes, but the Steering Committee will remain responsible for deciding which changes to adopt. The membership of this committee is: GA and JM. The committee will receive the first batch of data when trial participants are at a total of 50 along with information such as adverse effects, unforeseen circumstances and trial progress so far.

5.6.3 Funding

No participating centre will directly receive funds for involvement in TREC-Lebanon. By design, funding for the overall project is minimal. All funding is intramural and everyone involved is undertaking this project as part of their usual employment.

5.6.4 Proposed policy for publication and authorship

The success of the TREC-Lebanon trial depends on a collective collaboration of multiple people in different professions working in the hospital. As TREC-Lebanon trial is formulated as part of a PhD thesis program at the University of Nottingham, Joseph Dib is listed as primary author. However, due to the large number of people that may be involved in the study, general publication may not be able to name everybody that has contributed in minor ways to the study. Authorship will

depend on the substantial input onto the study. Every effort will be made to name everyone who has made such an effort within a collective authorship (the TREC-Lebanon Collaborative Group). The trial co-ordinator (JD) and research director of Deir Salib Hospital Souheil Hallit will meet to discuss principle authorships and potential journals of publication before final report is published.

5.6.5 Access to data

Once the study is completed, access to study and all its data will be anonymised and accessible as part of JD's final thesis draft. All data is protected as per regulations of the Psychiatric Hospital of the Cross and Lebanese Law.

5.7 Acknowledgments

5.7.1 Thanks

The authors acknowledge the work and efforts of the TREC-Collaborative Group – some not listed as authors - to which this trial took permission, acceptance, study design and initiative in order to carry out TREC-Lebanon.

The authors acknowledge the efforts of all employees at 'Deir Salib Hospital' Hôpital Psychiatrique De La Croix including all researchers, physicians, residents and nurses whose partaking in the trial made it possible.

The author acknowledges all the efforts of the University of Nottingham and in the Institute of Mental Health facility where this study was planned and passed onto ethics for approval.

5.7.2 Competing interests

The research co-ordinator JD declares none.

5.7.3 Prior beliefs

Clive Adams did not foresee a noticeable difference between HP and HPC while Joseph Dib believed HPC would have greater benefits than HP.

5.8 Appendix 1. TREC-Lebanon information for relatives

5.8.1 Information Leaflet

Dear Relative or Friend,

RE: TREC study (Rapid Tranquilisation Clinical Trial).

This hospital is taking part in the TREC study - helping to identify the very best treatment for agitated or aggressive people in an emergency situation. All drug treatments used in this hospital are safe, efficient, well established and familiar to the doctors and nurses. No one, anywhere in the world, knows which is the very best drug to use for the emergency situation in terms of speed of onset and recovery.

Once it is clear that your friend/relative is so disturbed/unwell that medication is needed, and the doctor looking after their care thinks them to be eligible for the TREC study, they are given one of two short acting sedating drug treatments (haloperidol + promethazine or haloperidol + promethazine + chlorpromazine). The choice of the treatment is made in fair, random, way, as in a lottery.

Participation in the study does not involve additional tests or examinations and everyone will receive the best care available. The TREC study has been approved by the Ethical Committee of Deir Salib Hospital.

If you want additional information, get in touch with TREC Collaborator in this hospital (Dr Souheil Hallit).

Thank you.

Joseph Dib

TREC Co-ordinator

5.8.2 Consent form

PATIENT CONSENT FORM

TREC-Lebanon

Division of Psychiatry & Applied Psychology
&
Psychiatric Hospital of the Cross

Dear friend,

You have been allocated to ***TREC-Lebanon*** – a trial studying two of the hospital's routine intervention drugs during emergency periods requiring rapid tranquilisation. While you were in a state of agitation, you were allocated to either a group receiving haloperidol + promethazine or haloperidol + promethazine +chlorpromazine. This trial is designed to see which, if any, of the groups work most efficiently.

As your participation was involuntary, you may still change your mind about being involved. You are free to withdraw at any point post reading this form but not after data has been collected and anonymised as the trial co-ordinator will not know who you are. Withdrawal does not require a reason.

What is the project about?

The project is looking at rapid tranquilisation between two of the hospital's routine interventions, and which works best.

Who is being asked to take part, and why?

Clinicians – that is doctors and nurses as they are part of the routine care treatment.
Patients – that is patients exhibiting an aggressive episode requiring rapid tranquilisation.

Has the research been of any personal benefit to me?

Yes, either interventions you may have received are aimed at calming you down during a state of aggression.

What will you do with the data?

Once data has been collected, they will be anonymized by the lead researcher and inputted onto a transcription form whereby they will be analyzed in order to see differences between both intervention groups.

If you have any questions or concerns, please don't hesitate to ask.

If you are interested in the results of the survey or if you wish to withdraw your data from ***TREC-Lebanon***, please contact the head researcher (contact details below)

THANK YOU FOR YOUR PARTICIPATION

Head Researcher: Joseph Dib
(joseph.dib@nottingham.ac.uk)
Hospital Research Director: Dr. Souheil Hallit
(souheilhallit@hotmail.com)

If you have any queries or complaints about this study, please contact the head researcher at the first instance.

If this does not resolve the query to your satisfaction, please write to the Administrator to the Division of Psychiatry & Applied Psychology's Research Ethics Sub-Committee (MS-DPAPEthics@nottingham.ac.uk, +44 (0)115 8232214) who will pass your query to the Chair of the Committee.

This study has been ethically approved by both the University of Nottingham and the Psychiatric Hospital of the Cross.

5.9 Appendix 2. TREC-Envelope entry form - completed blind to treatment of allocation

5.9.1 TREC Entry Form

Please answer the questions before you open the envelope, and leave the completed envelope in the TREC-Bin box

TREC Number: ☐

Bulletin/Medical Notes number: ☐

Patient's Name: ☐

How disturbed is this Person? ☐ Number (Choose only one option)

1- Moderately
2- Markedly
3- Extremely
4- One of the most disturbed people you have seen
5- Other, Please describe ☐

In your opinion, which is the primary cause of this episode? ☐ Number (Choose only one option)

1. Psychosis
2. Intoxication
3. Dementia
4. Mental retardation
5. Other organic problem. Which one? ☐
6. Psychological distress
7. Unknown
8. Other. Which one? ☐

Further details: ☐

Time of completing this form: hh ☐ mm ☐

Signature: ☐

5.10 Appendix 3. Primary outcome

TREC number

Medical no.

Follow up Form

Please take care completing this, Accuracy is important

Time of administration

Hour Minutes

	Calm or tranquil?	Asleep?	Straitjacket +/- Restraint?	Important adverse effects?	Left the ward?
20 minutes after TREC medication					
40 minutes after TREC medication					
60 minutes after TREC medication					
2 hours after TREC medication					

Have important adverse effects occurred? Yes No

If 'Yes', please describe which occurred, and when.

Other comments

Thank you.

TREC number

5.11 Appendix 4. Dr. Stopwatch Form

Dr. Stopwatch form

When the person arrives in the Emergency Room observe the situation.

When the person is given the TREC medication start the watch.

Time person was tranquilised

Tranquilisation = when you feel the person is peaceful (whether asleep or not).

Time person fell asleep

Any other comments

5.12 Appendix 5. Serious event form

TREC number

Serious Event Form

This form should be used to immediately notify the TREC Co-ordinator of any events that are serious and unexpected.

Details of unexpected serious event – when started, when ended, management, outcome

Patient’s name	Name of responsible clinician
Hospital name	Bulletin or notes number
Signature of person completing form	Date form completed

Please fax the completed form to the TREC Co-ordinating Centre.

If fax is not possible, please communicate as soon as possible the local collaborator.

Thank you

Joseph Dib

TREC Co-ordinator

ADDRESS

TEL:

FAX:

E-mail: msxjd6@nottingham.ac.uk

5.13 Appendix 6. TREC-Lebanon Main data collection form

Data transcription form

Initial data

Date of collection			
	day	month	year
Time of collection			
	hour	minutes	
TREC number			
ER / medical notes number			
Patient's name			
Sex			
	M / F		
Date of birth			
or	day	month	year
Approximate age		years	
Cause of agitation		Transcribe the number on the TREC envelope	
Diagnosis			
Severity of agitation		Transcribe the number on the TREC envelope	
Date TREC envelope was opened			
	day	month	year
Time TREC envelope was opened			
	hour	minutes	

Name of person who opened the TREC envelope	

TREC drug(s) ☐
H+P / HPC

Drug(s) given during the first 24 hours

Name of drug	Dose	Route of administration*	Time	
				hourminutes
				hourminutes
				hourminutes
				hourminutes
				hourminutes
				hourminutes
				hourminutes
				hourminutes

			hour	minutes

			hour	minutes

* If oral, register only the time of first administration and the frequency that the drug was to be given, eg. Twice/day or four times/ day

Were oral drugs refused in the first 24 hours?		Yes / No / Not applicable (not perscribed oral medication)

All these data should be on the prescription form. Is there anything you want to add? Please note it here.

Emergency Drug(s) given during the first 24 hours

Name of drug	Dose	Route of administration*	Time	
			hour	minutes
			hour	minutes
			hour	minutes

			hour	minutes
			hour	minutes
			hour	minutes
			hour	minutes
			hour	minutes
			hour	minutes

* If oral, register only the time of first administration and the frequency that the drug was to be given, eg. Twice/day or four times/ day

Were oral drugs refused in the first 24 hours?		Yes / No / Not applicable (not prescribed oral medication)

All these data should be on the prescription form. Is there anything you want to add? Please note it here.

TREC Number	
First psychiatric attendance?	

	Yes / No / Unknown
Already on antipsychotics?	

	Yes / No / Unknown
Where did the patient go immediately after administration of TREC drugs?	

1-Transferred to ward

2- Left the ward

3- Transferred to another hospital

4- Other

In case of 'Ward of another hospital', which hospital?	

In case of 'AWOL', at what time did		

the patient go AWOL?	Hour / Minutes
In first the 24 hours after the use of TREC drugs, was the doctor was called to see the patient?	Yes / No / Unknown
Have important adverse reactions been registered on the notes or chart within the first 24 hours?	Yes / No / Unknown

If they have been registered…

Type of reaction	Approximate time
	hour / minutes

	hour	minutes
	hour	minutes

How were the adverse effects managed?

All this information should be in the notes or ER chart. If there is anything you would like to add, please write it here.

	Which one?
Do the notes record a diagnosis for this episode?	
Were there other episodes of aggressiveness in first the 24 hours?	Yes / No

If so….

day	month	hour	minutes

Calm or Tranquil	20 minutes/ 40 minutes/ 60 minutes/ 2 hours
Asleep	20 minutes/ 40 minutes/ 60 minutes/ 2 hours
Straitjacket+/-	20 minutes/ 40 minutes/ 60 minutes/ 2 hours

Restraint	20 minutes/ 40 minutes/ 60 minutes/ 2 hours
Important adverse effects?	20 minutes/ 40 minutes/ 60 minutes/ 2 hours
Left the ward?	20 minutes/ 40 minutes/ 60 minutes/ 2 hours
Was the doctor called?	Yes/ No/ Unknown

Any other comments	

Please, staple this to the primary outcome form, and give it to Joseph Dib.

Thank you.

5.14 Appendix 7. Dummy Tables

5.14.1 Dummy table A. Characteristics of patients at trial entry

	Haloperidol + Promethazine (n = …)	HPC (n = …)
Mean age (SD)		
Sex Male Female		
First psychiatric attendance Yes No Unknown		
*Severity of disturbance - first impression moderately markedly severely among the most extremely disturbed		
*Presumed cause for agitation Psychosis (schizophrenia or mania) Substance abuse Mental organic (dementia or oligophrenia) Clinical organic (metabolic, hormones, etc) Psychological Unknown		

* before opening the TREC envelope

5.14.2 Dummy table B. Compliance with the allocated treatment, and additional medication

	Haloperidol + Promethazine (n = …)	HPC (n = …)
Already on antipsychotics?		
Yes No		
Allocated treatment		
No allocated treatment		
Non-Emergency Drugs in the first 24 hours (doses?)		
None		
Drug		
Drug		
Drug Drug Drug		
Emergency drugs in the first 24 hours (by class and route of administ)		
None		
Drug		
Drug Drug Drug		
Immediate placement		
Transferred to ward		
Left the ward		
Transferred to another hospital Other		

5.14.3 Dummy table C. Primary measures of outcome

	Haloperidol + Promethazine (n = …)	HPC (n = …)
Tranquillisation		
% Tranquilised (Calm/Tranquil)		
By 20 minutes		
By 40 minutes		
By 60 minutes		
By 2 hours		

5.14.4 Dummy table D. Secondary measures of outcome – first 24 hs

	Haloperidol + Promethazine (n = …)	HPC (n = …)
Tranquilisation (Calm or Tranquil after second agitated episode)		
% tranquillised after 2 hours		
Sleep		
% asleep By 20 minutes By 40 minutes By 60 minutes By 2 hours		
Straitjacket +/- Restraint Indicate whether patient had straitjacket only or included restraint		
% needing physical restraints after TREC drugs		
Mean time in physical restraints (SD)		
Revved Up Episode (Same agitated episode at different time Interval)		
By 20 minutes By 40 minutes By 60 minutes By 2 hours		
Second Agitated Episode (Agitated episode post 2 hours)		
Drugs used - by class and route of administration		
Adverse reactions		
Acute dystonia Mental confusion Akathisia (motor restlessness) Problems with vital signs Other		
Immediate placement		
Transferred to ward		
Left the ward		
Transferred to another hospital Other		
Was the doctor called?		
Yes No Unknown		

5.14.5 Dummy table E. Clinical progress / service outcomes / 2 weeks

	Haloperidol + Promethazine (n = …)	HPC (n = …)
Diagnosis (If applicable)		
Diagnosis at 2 weeks or diagnosis at time of discharge, if that was before 2 week		
Length of stay – time to discharge		
% discharged		
by 1 week		
by 2 weeks		

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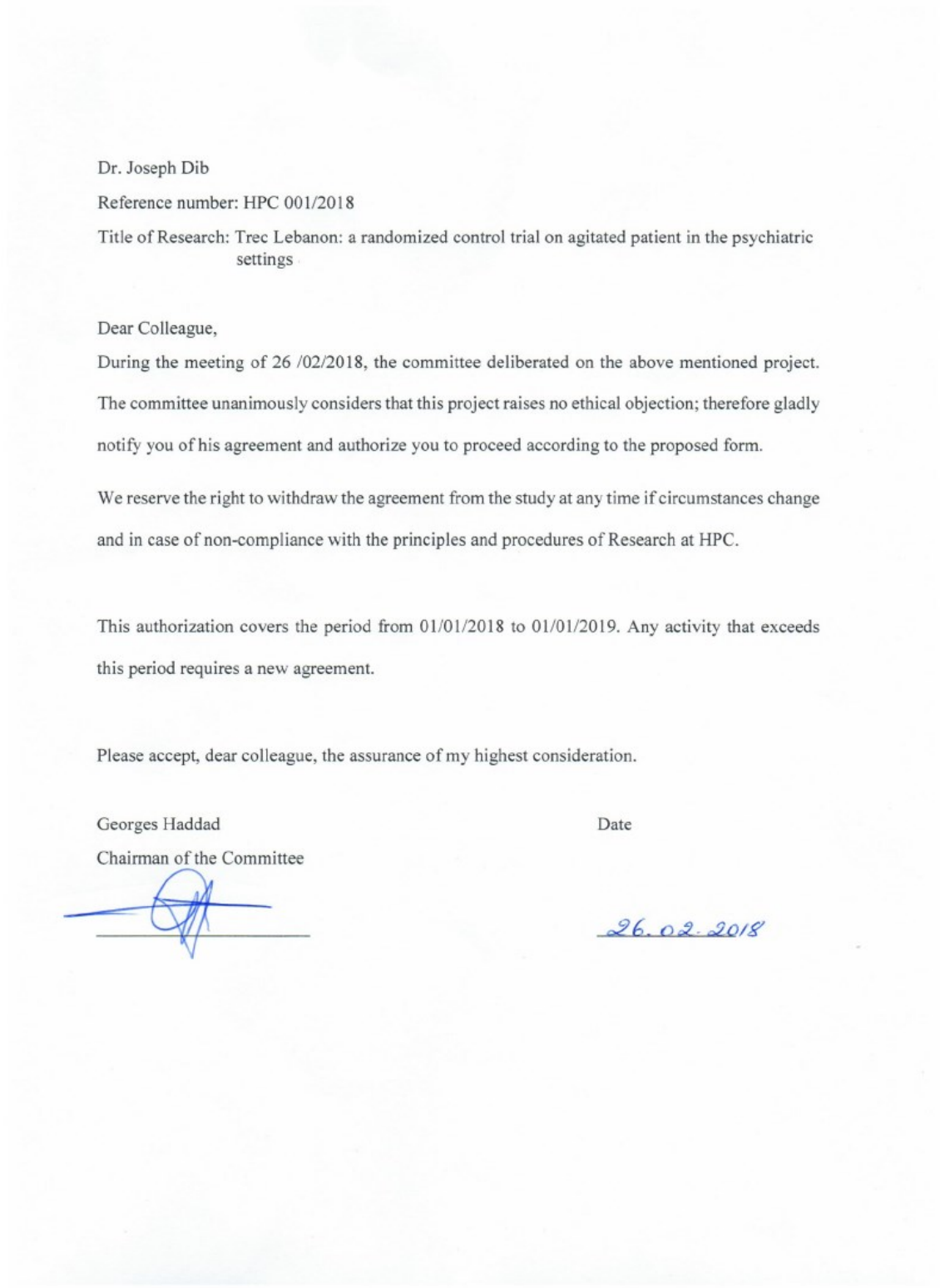
5.16 Ethics Forms

5.16.1 Lebanese document from chairman of the committee

Figure 0.4: Lebanese ethics form



Dr. Joseph Dib

Reference number: HPC 001/2018

Title of Research: Trec Lebanon: a randomized control trial on agitated patient in the psychiatric settings

Dear Colleague,

During the meeting of 26 /02/2018, the committee deliberated on the above mentioned project. The committee unanimously considers that this project raises no ethical objection; therefore gladly notify you of his agreement and authorize you to proceed according to the proposed form.

We reserve the right to withdraw the agreement from the study at any time if circumstances change and in case of non-compliance with the principles and procedures of Research at HPC.

This authorization covers the period from 01/01/2018 to 01/01/2019. Any activity that exceeds this period requires a new agreement.

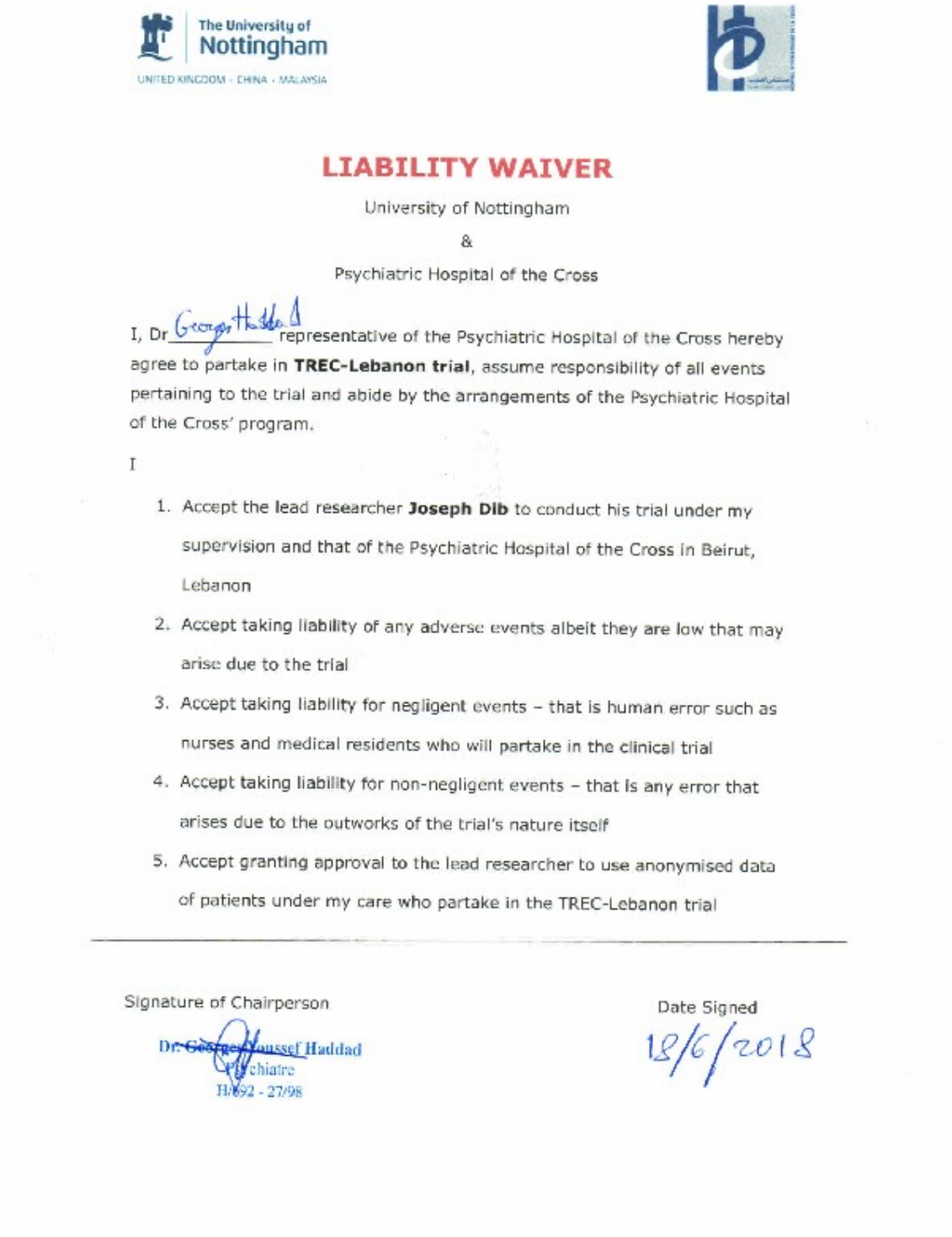
Please accept, dear colleague, the assurance of my highest consideration.

Georges Haddad — Date

Chairman of the Committee

26.02.2018

Figure 0.5: Liability waiver



The University of Nottingham
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LIABILITY WAIVER

University of Nottingham

&

Psychiatric Hospital of the Cross

I, Dr George Haddad representative of the Psychiatric Hospital of the Cross hereby agree to partake in **TREC-Lebanon trial**, assume responsibility of all events pertaining to the trial and abide by the arrangements of the Psychiatric Hospital of the Cross' program.

I

1. Accept the lead researcher **Joseph Dib** to conduct his trial under my supervision and that of the Psychiatric Hospital of the Cross in Beirut, Lebanon
2. Accept taking liability of any adverse events albeit they are low that may arise due to the trial
3. Accept taking liability for negligent events – that is human error such as nurses and medical residents who will partake in the clinical trial
4. Accept taking liability for non-negligent events – that is any error that arises due to the outworks of the trial's nature itself
5. Accept granting approval to the lead researcher to use anonymised data of patients under my care who partake in the TREC-Lebanon trial

Signature of Chairperson

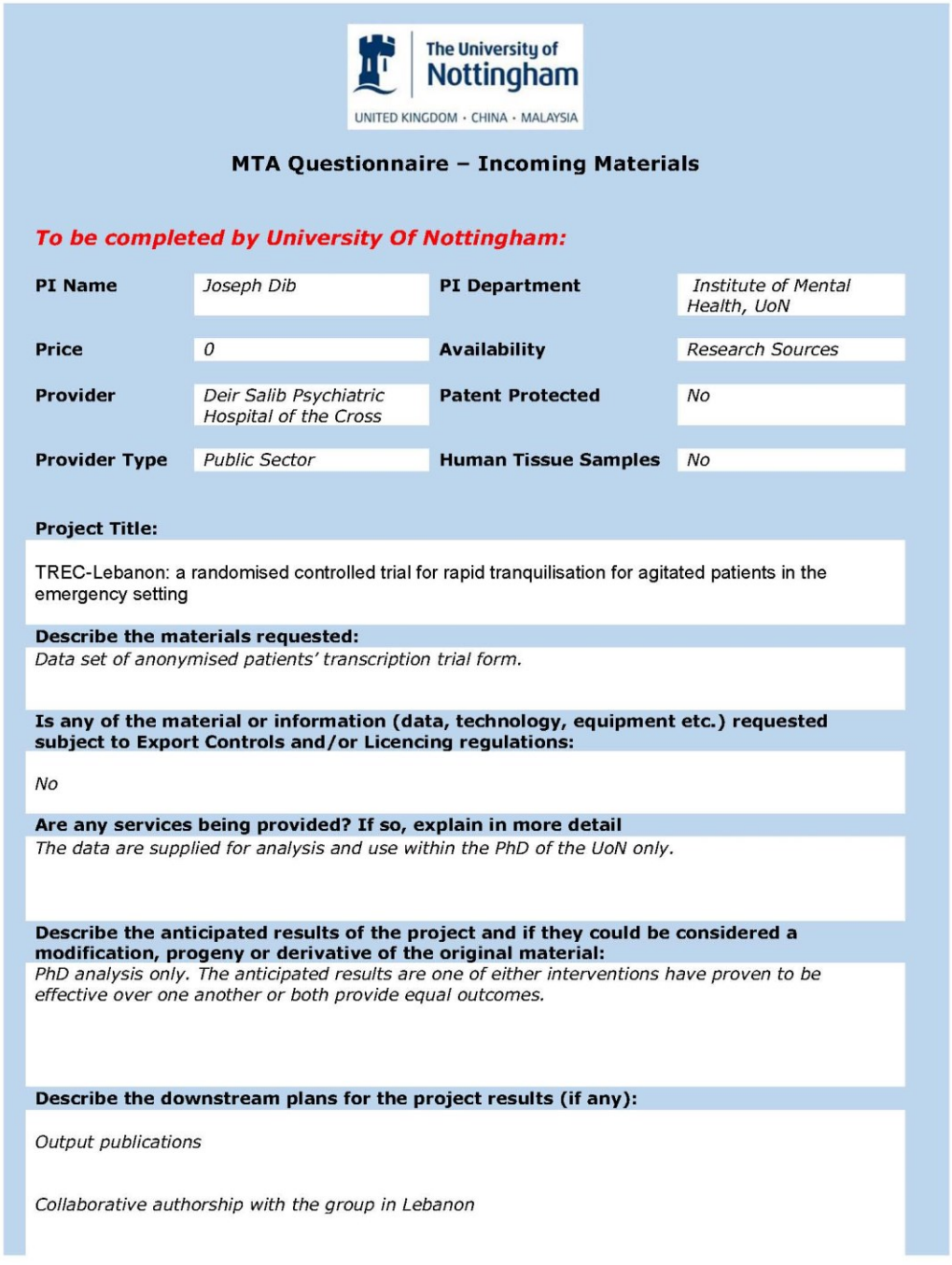
Dr. Georges Youssef Haddad
Psychiatre
H/692 - 27/98

Date Signed

18/6/2018

5.16.2 University of Nottingham ethics

Figure 0.6: MTA questionaire



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MTA Questionnaire – Incoming Materials

To be completed by University Of Nottingham:

PI Name	*Joseph Dib*	**PI Department**	*Institute of Mental Health, UoN*
Price	*0*	**Availability**	*Research Sources*
Provider	*Deir Salib Psychiatric Hospital of the Cross*	**Patent Protected**	*No*
Provider Type	*Public Sector*	**Human Tissue Samples**	*No*

Project Title:

TREC-Lebanon: a randomised controlled trial for rapid tranquilisation for agitated patients in the emergency setting

Describe the materials requested:

Data set of anonymised patients' transcription trial form.

Is any of the material or information (data, technology, equipment etc.) requested subject to Export Controls and/or Licencing regulations:

No

Are any services being provided? If so, explain in more detail

The data are supplied for analysis and use within the PhD of the UoN only.

Describe the anticipated results of the project and if they could be considered a modification, progeny or derivative of the original material:

PhD analysis only. The anticipated results are one of either interventions have proven to be effective over one another or both provide equal outcomes.

Describe the downstream plans for the project results (if any):

Output publications

Collaborative authorship with the group in Lebanon

Any factors that we should be aware of (e.g. time pressures, funder obligations, third party requiring access to materials):

All needs to be done within an adequate time frame in respect with the PhD timetable.

Please return completed to *BB-Contract-Request@exmail.nottingham.ac.uk*

Information to be requested from Provider

Contact Details of the PI/Lead Scientist and Contracts Officer (or equivalent):

PI/Lead Scientist's full-name:	Dr. Georges Haddad
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Contracts Officer (or equivalent):	Dr. Souheil Hallit
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