Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

Phase 1 studies and The Over-Volunteering Prevention System (TOPS)

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Approved by (name & role)	Dr Dipak Patel, Research Manager	**Date**	21 May 2018
Signature:			

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Phase 1 studies and The Over-Volunteering Prevention System (TOPS)

This SOP has been produced in accordance with Health Research Authority (HRA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) Phase 1 accreditation scheme. This SOP will outline the procedure for registering healthy volunteers with TOPS for all Phase 1 research studies undertaken at Sheffield Teaching Hospital NHS Foundation Trust (STH).

1. Background

Healthy volunteers who take part in clinical trials are commonly compensated financially for their participation. There exists a need to monitor participation in clinical trials for the safety and protection of these individuals. Healthy volunteers who participate recurrently in clinical trials of new and novel interventions place themselves at risk. Healthy Volunteers seldom derive therapeutic benefit from taking part in a clinical trial, so the risk of harm must be kept at a minimum. There are various medical, scientific and ethical reasons to obviate healthy volunteers from participating in too many trials, such as:

- It is unethical to expose healthy people too often to medicines they don't need
- If the gap between trials is too short or there is an overlap, the medicines used in the trials may interact
- Taking too many blood samples can cause anaemia
- It may be dangerous to expose healthy people to radiation that is not necessary or have more doses than is safe

Boyce *et al* (2012) of the Hammersmith Medical Research Phase I Unit produced data which indicated that 1 in 10 healthy volunteers screened at the unit between 1997 to 2001 had completed a study of an investigational medicinal product within the previous 12 weeks despite signing a declaration to state the opposite. Through this finding they developed 'The Over-volunteering Prevention System (TOPS)'. Following the inception of this database and in line with the Health Research Authority (HRA), the MHRA accreditation scheme and as a standard condition of ethical approval, healthy volunteers undertaking Phase 1 studies would need to be registered with The Over-Volunteering Prevention System (TOPS). TOPS is a database which is free to all UK organisations undertaking Phase 1 studies. It aims to prevent participants from taking part in trials too frequently.

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2. Acronyms

CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
HRA	Health Research Authority
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare Products Regulatory Agency
PI	Principal Investigator
STH	Sheffield Teaching Hospitals NHS Foundation Trust
TOPS	The Over-volunteering Prevention System

3. Definitions

The Over-Volunteering Prevention System is a database, free to all UK organisations undertaking phase 1 trials in healthy volunteers, that aims to prevent participants from taking part too often in trials of new medicines. TOPS was formerly run by an independent charity, but in April 2013, its function has come within the remit of the HRA. TOPS allow investigators to identify a volunteer, and to determine when he/she was last registered to take part in a Phase I trial. The database is designed to detect most cases of accidental or deliberate over-volunteering, but it is not designed to detect professional over-volunteering or fraud.

Upon creating a TOPS account an investigator will be classed as a "site admin user". A site admin user will have the ability to register new volunteers, search for volunteers who have already been registered and to update existing records for volunteers. Once a TOPS account is created it will be possible to register a volunteer on the system. Consent must be obtained from the volunteer in order to store their details in the database. The key information to enter is listed within the procedure below. The TOPS system does not allow an investigator to search openly for a volunteer. A volunteer must be first registered against Sheffield Teaching Hospitals NHS Foundation Trust (STH), which as discussed requires consent. Once a volunteer is registered against STH an investigator can search and check whether the volunteer is participating in a study at other units. A volunteer will be identifiable within TOPS through their passport number or National Insurance Number.

4. Procedure – STH Hosted studies

4.1 As discussed in the background section of this SOP it is a requirement that healthy volunteers taking part in Phase 1 studies be registered on the TOPS database.
4.1.1 The Principal Investigator (PI) or delegate registers with TOPS to get a user name and password from if they do not already have one. This will allow the PI to be a registered site admin user for TOPS.

4.2 Healthy volunteer registration on TOPS requires a unique identifier such as their National Insurance (NI) number or passport number and country of origin if the passport is non-UK. When booking an initial study visit with the volunteer the Investigator must instruct the volunteer to bring either an NI card, a document confirming the NI number or a valid Passport with them to their first visit and each subsequent study visit.

4.3 When discussing the trial with the healthy volunteer the PI or delegate should explain the reason for TOPS and must gain the written consent of the healthy volunteer to enter their details on the TOPS database.
4.3.1 Following consent of the healthy volunteer the PI or delegate must ensure the consent form is filed in the healthy volunteer research notes. If the healthy volunteer already has a set of STH medical notes this information will be documented there. A photocopy of their NI number/passport number will also need to be made and kept as supporting evidence.
4.3.2 If the healthy volunteer refuses to consent to being placed on the TOPS database they must be automatically excluded from the study and advised accordingly of the reasons.
4.3.3 The PI or delegate must enter details of the participant and current study (using the IRAS ID) onto the TOPS database immediately following consent. This must be done before the volunteer is confirmed as eligible, randomised or dosed.

4.4 Once the volunteer has been registered on the TOPS database the PI or delegate must check the volunteer's TOPS history and identify any previous registrations recorded for other phase I trials. A TOPS entry will include details of the dates of participation, date of last dose and the appropriate follow up period. If the healthy volunteer is attempting to take part in a further phase I trial within the specified follow-up period of the previous trial (thus causing an overlap) then PI must halt inclusion into the study until the follow up period is complete. It may also be necessary to contact the research team from the previous study if key information, such as

'date last dosed' is missing from the TOPS entry. This information should be clearly explained to the healthy volunteer and must be documented in the healthy volunteers' notes.
4.4.1 Should the healthy volunteer be excluded from the current study, an explanation should be provided to them by the PI or delegate.
4.4.2 The PI may (using their own discretion) also decide to delay the recruitment of the healthy volunteer until a reasonable time has elapsed since the completion of the follow-up period identified in the previous study.
4.4.3 If there are no safety concerns arising, the healthy volunteer can then undergo eligibility checks with a view to being enrolled/randomised.

4.5 Once the healthy volunteer is enrolled onto the trial each treatment episode within the phase I trial and the date of the last dose of the IMP must be entered onto the TOPS system.
4.5.1 The PI or delegate should ensure that this information is entered into TOPS promptly.
4.5.2 The TOPS system is intended to record accurate dates to ensure that the healthy volunteer's safety is paramount.

5. Procedure – STH Sponsored studies

5.1 It is the responsibility of the R&D Coordinator to identify an STH Sponsored CTIMP upon registration with the Research Department. The R&D Coordinator will then highlight the potential requirement for use of TOPS to the Chief Investigator (CI) if the trial involves healthy volunteers.

5.2 When drafting the study protocol it is the responsibility of the CI to specify that healthy volunteers must consent to be added to TOPS within the inclusion/exclusion criteria.

5.3 When drafting the Participant Information Sheet (PIS) and the Informed Consent Form (ICF) it is the responsibility of the CI to ensure that these documents will obtain and record the volunteers' permission to allow them to be registered on TOPS. The HRA provides guidance which recommends explicit wording which can be used on the PIS and ICF. This can be found on the HRA website. The TOPS information and consent statements can be included in the main PIS/ICF or a separate PIS/ICF may be created and included in the REC/HRA submission.

5.4 For guidance relating to the procedure to follow when the study is open please refer to steps 4.1 – 4.5 as described for hosted studies.

5.5 Other units may contact the research team requesting information regarding the current study if the healthy volunteer subsequently consents into another study.
5.5.1 The CI must ensure that all relevant information is passed on to the study team making the enquiry to ensure that the healthy volunteer's safety is considered.
5.5.2 All conversations must be documented fully in the healthy volunteer's research notes

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