

# Recruitment of Volunteers in Early Clinical Trials

a report by

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Post and Organisation

## Introduction

Pharmaceutical productivity is declining as deemed by the number of new marketing authorisations in the US and the EU during the last few years. There are several reasons for this: stronger regulatory demands on safety and efficacy, more competition and the increasing cost of developing new medicines. To get safer medicines faster is now an aim for both the pharmaceutical industry and the regulatory authorities (such as the European Medicines Agency's Innovative Medicines Initiative, Federal Drug Administration's Fast track). For the industry it is important to get to milestones as early as possible as >90 % of the new chemical entities (NCEs) entering phase 1 will fail to be launched. The disaster at Northwick Park Hospital, London, adds to a complex situation where it is increasingly hard to find volunteers for early clinical studies.

## Recruitment in Early Trials

After the tragedy with the healthy volunteers testing a CD6 targeted drug activating the immune system at the research unit at Northwick Park Hospital in London, one would assume that there has been a drop in the number of volunteers showing interest in participating in clinical trials. However, this is not the case at the Trial Form Support (TFS) Phase 1 unit at the Clinical Research Centre (CRC) at Karolinska University Hospital in Stockholm, Sweden. The phase 1 unit is contacted by 10-15

new healthy volunteers per day who can be added to the database of 1,500 volunteers, without any advertisement or active recruiting measures from the unit.

The key to this success is the partnership between academia and the healthcare industry, by combining the expertise of Europe's top medical university hospital with Europe's top contract research organisation (CRO). Both partners can concentrate on their own specialities. Aside from the technical resources, the TFS phase I unit can provide their clients with the hospital's collective knowledge, academic research experience and therapeutic insights. Also, for academia this is a win-win situation as the clinical researchers at the hospital encounter a wide range of new treatment modalities early on and are offered the possibility of reporting interesting scientific papers. The university hospital is also the given the opportunity to perform studies for companies in countries like the US, Japan and India, who probably would not have contacted the hospital otherwise. The customers naturally benefit from this bilateral combination of regulatory and medicinal expertise.

## Cutting Numbers in Phase 1 Studies with the use of Phase 0 Studies

The TFS phase I unit has unique experience in a great variety of studies in 'phase 0' studies with positron emission tomography (PET) camera in microdose or titrating to full dose, with or without magnetic resonance imaging (MRI). This means that phase 1 studies in central nervous system (CNS) active molecules to evaluate receptor occupancy and determine pharmacokinetics and pharmacodynamics (PK/PD) minimise the need for numbers of volunteers in later ordinary phase 1 programmes and thereby reduce the time to reach proof of concept studies, the most important clinical milestone. Other studies typically performed at the unit are first in man studies with single dose and multiple (increasing) dose administration, bioavailability and bioequivalence studies, drug interaction studies, food interaction studies, studies in obesity, diabetes and a number of proof of concept studies. The variation of studies also leads to a variation of volunteers from healthy volunteers to special populations. The number of participants varies from a few participants in PET studies to larger numbers in bioequivalence studies. Many drug developing companies, both big pharma and biotech, also call for early inclusion of female volunteers to cover gender aspects, which is possible with the large pool of healthy volunteers stored in the database, after appropriate research ethical board approval.

## Quality Assurance

The unit has put in place a quality system for follow-up of the subject experiences, and is also participating in the hospitals patient safety surveillance programme. In addition to the full security and surveillance



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equipment in the phase I unit the unit is located at the heart of the Hospital, 50m from the intensive care unit and emergency room. There is also a well established collaboration with the anaesthesiologists, among other disciplines. The unit is regularly monitored and audited by customers, partners and internal quality controllers.

The main ingredient in this collaboration between a CRO and academia is the transparent and frequent communication that enables the smooth working relationship between the organisations. While academia typically works at a slower pace, the CRO is pressed by demands from customers and competent authorities, as well as time and cost constraints. As there is no generic standard for recruiting volunteers, the recruitment differs between populations (and studies). To meet these demands academia contributes with knowledge and impacts on the recruiting procedures, from healthy volunteers to special patient populations.

### Cutting Time

With time constraints and new regulatory approaches it is more common today to cut time to proof of concept studies. One way to do this, after receiving scientific advice from a competent authority, is to put detailed PET studies in place, and thereafter directly performing PK/PD in patient cohorts (phase IIa). Particularly in CNS active molecules this has been a successful way to cut time and costs. Including spiral computed tomography (CT) and/or MRI the same technique is useful also in substances active on peripheral receptors.

The Northwich Park Hospital disaster led to the Professor Duff Commission in the UK and their 22 commandments on early clinical testing of new drugs. This has led to a new praxis coming up, probably soon to be realised in new European Medicines Agency (EMA) guidelines. It will lead to fewer subjects tested in each batch and more sophisticated technical and logistic measures. Online monitoring of the drug and faster PK analyses in dose-escalating studies may become more important. This increase on safety demands will assure presumptive volunteers that all possible means to protect them are undertaken, and guarantees successful future recruitments.

This means also that in the future, even more so in dose-escalating studies, it may not be possible to withdraw PK samples for storage in freezers and analysis post-study, but rather establishes the need to use online monitoring and good laboratory practice (GLP) standards in phase I testing for dose adjustments in titrating and dose-escalating studies. For this reason the TFS phase I unit has now contracted the Karolinska University Laboratory to establish drug analysis by liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) on an online basis. All work at the laboratory is carried out according to GLP. For pharmacokinetic studies this is a great advantage when it is necessary to perform pharmacokinetic calculations and present results during the study, for decisions on upcoming dosing and titration. It also reassures the volunteers that each dosing step is carefully examined and calculated before performed.

### What Volunteers are Being Sought?

There is a positive attitude among laymen in Sweden towards participation in clinical trials. The compensation for participation is generally low and not attractive enough for students and the unemployed. Questionnaires to people in the author's registry indicate

that the majority of the volunteers want to participate in clinical studies to 'do good', or to 'improve medical knowledge'. For this reason volunteers consist of a representative sample of the people in the Stockholm area, young and old; healthy and diseased; male and female; and of different ethnic origins. Moreover, with a mandatory and unchangeable social security number, everyone is retrievable for unforeseen follow-ups, and may be called in many years after the study for further checks, if necessary.

However the establishment in hospitals of specialised units for clinical research seems to be a successful way to ensure recruitment is done according to plan. The collaboration between the hospital, academia and a CRO ensures focusing on targets, and academia has an important role in avoiding excess marketing and securing the safety of the subjects, while at the same time learning logistics, good clinical practice and the regulatory environment. The scientific pace speeds up somewhat after the learning phase.

### Screening Sites

The vision for the future for the TFS phase I unit at Karolinska University Hospital is to help customers and clinics to find patients to do screening for phase 2 and 3 studies and to enlarge the phase I unit into a 'screening site'. Sometimes these patients are only mildly ill, and can be found in through general practices rather than in the University Hospital. This recruitment can be done by data mining in diagnostic registers to find out about the frequency of a certain illness in the region, followed by advertising in local papers, where those who are interested can contact call-centres with medically trained staff that use questionnaires for a preliminary screening of candidates. If the outcome is positive, the person is then referred to the 'screening site'. Here the potential volunteer is given full information and if accepted, gives his/her consent. The final selection is the made by the investigator after appropriate testing according to protocols. Since all applicants are carefully pre-screened, the investigators save considerable time and hassle, and clients meet their inclusion needs in a speed often exceeding estimates. If patients are randomised to a study general practitioners will be informed when required. However, this procedure is not mandatory in Sweden.

### Conclusion

The world renowned Karolinska Institute is one of Europe's largest medical universities. Since 1901 the Karolinska Institute has been honoured with awarding the Nobel Prize in Physiology or Medicine. This has given the Karolinska Institute an invaluable contact network throughout the medical scientific community. Research at Karolinska University Hospital is carried out within all clinical disciplines - from basic to translational and applied research. TFS is a Swedish CRO, with affiliates all over Europe. It has been awarded several commercial prizes for its growth, financial strength and strategic expansion. The TFS phase I unit is located in the clinical research centre at Karolinska University Hospital in Stockholm, Sweden. ■