PhUSE 2007

Paper MT02

WEB-TRIAGE
An application for patient registration in phase I dose-escalation studies

Angelo Tinazzi, Alessandro Cattaneo, SENDO-Tech S.r.l., Milan, Italy
Lucio Ferraresi, Paolo Ferroni, Eventi Telematici, Milan, Italy

ABSTRACT

Phase I clinical trials conducted to find recommended doses for use in later phase studies, employ pre-specified guidelines. These determine what dose to administer to the next subject or group of subjects. "Standard" Phase I trials (in oncology) use what is often called the '3+3' design, where at least 3 patients are treated at each dose level (dose L), by applying the following rules:

- If 0 patients experience dose-limiting toxicity (DLT), escalate to dose L+1;
- If 2 or more patients experience DLT, de-escalate to level L-1;
- If 1 patient experiences DLT, treat 3 more patients at dose level L;
    - If 1 of 6 experiences DLT, escalate to dose level L+1;
    - If 2 or more of 6 experiences DLT, de-escalate to level L-1;

Most phase I trials in oncology are multi-institutional (MI). Recent research have investigated accrual data from published phase I clinical trials and it emerged that MI Phase I are associated with an increased number of patients and a trend toward increased accrual time[1].

In addition sequential patient accrual is used within and between L to prevent potential DLTs "clustering" and protect patients from undue exposure to toxic dose overshooting. Thus, triage strategies are commonly used to streamline and coordinate accrual.

We therefore developed a web-based application (WEB-Triage) to:

- design specific study patient registration form;
- propose potential candidate for next available "slot" (the Investigator);
- reviewing candidates and eventually accept or reject the registration;
- opening or closing dose levels by applying the above rules;
- manage concurrent dose-escalation clinical trials

The application was developed using Microsoft ASP.NET 2.0 and MS SQL Server 2005 on an IIS (version 6.0) Web Server; HTTPS SSL 128/256 bit was used for data-encryption.

INTRODUCTION

Traditional phase I clinical trials are designed to evaluate the dosing and toxicities of novel agents (phase I) or combination of agents (phase Ib) in humans after appropriate preclinical (and clinical for phase Ib) testing of toxicology, pharmacology and safety; the ultimate goal is to determine the appropriate dose for use in phase II trials.

THE METHODOLOGY OF PHASE I DOSE ESCALATION TRIALS IN ONCOLOGY

The main difference between phase I trials in oncology with respect to most other therapeutic areas is that the subjects on study are patients and not healthy volunteers. However, patients eligible for phase I studies usually have advanced disease failing standard therapies or for whom no effective treatments exists, yet continue to be functionally well.

Phase I trials in oncology come In many 'flavours'. So far the most common type has been phase I trials of new cytotoxic drugs where the starting dose is not expected to cause severe toxicity and is determined on the basis of animal toxicology studies, usually tenth of the median lethal dose (LD_{10}) in the most sensitive animal species. The dose is increased in subsequent patient cohorts according to preplanned dose levels. Dose escalation occurs only after sufficient time has passed to observe acute toxic effects in patients treated at lower doses. Cohorts of three to six patients are treated at each dose level. Usually, if no dose limiting toxicity - DLT is seen in the first 3 patients treated at a given dose level, the dose is escalated in the next cohort. If the incidence of DLT is one third, then three more patients are treated at the same level. If no further cases of DLT are seen in the additional patients, then dose escalation can continue. Otherwise, if 2 or more out of 3 to 6 patients experience DLT, dose escalation is stopped (maximum tolerated dose – MTD). The phase II recommended dose – RD, is often defined as the highest dose for

which the incidence of DLT is less or equal 33%. Usually six or more additional patients are treated at the RD to confirm its tolerability.

The pre-determined dose-levels, are commonly based on a 'modified Fibonacci series'[2]. Dose increments are by 100% at level 2, 67% at level 3, 50% at level 4, 33% at level 5 and following levels (see example in Table 1). There is no scientific basis for this approach, except that experience has shown it to be safe and effective. In some cases it results in having to explore many dose levels before the MTD is found. It also may provide an imprecise estimate of the MTD and it varies among patients[3]. Other approaches have been proposed to overcome some of these limitations.

There are several other type of phase I trials. Some phase I trials are pilots for phase III trials, exploring one to three dose levels of a drug combination; in some cases phase I trials attempt to answer comparative questions, for example if drug A should be administered before or after drug B in a two-drug combination and in other cases they try to answer multiple questions, such as reccomended dose and schedule (Figure 1).

Dose level (cohort)	Dose increment	Dose (mg/m^2)
1	Starting dose	0.10
2	100%	0.20
3	67%	0.33
4	50%	0.50
5	33%	0.67
6	33%	0.89
7	33%	1.18
8	33%	1.57
9	33%	2.08

Table 1: Example of dose escalation protocol

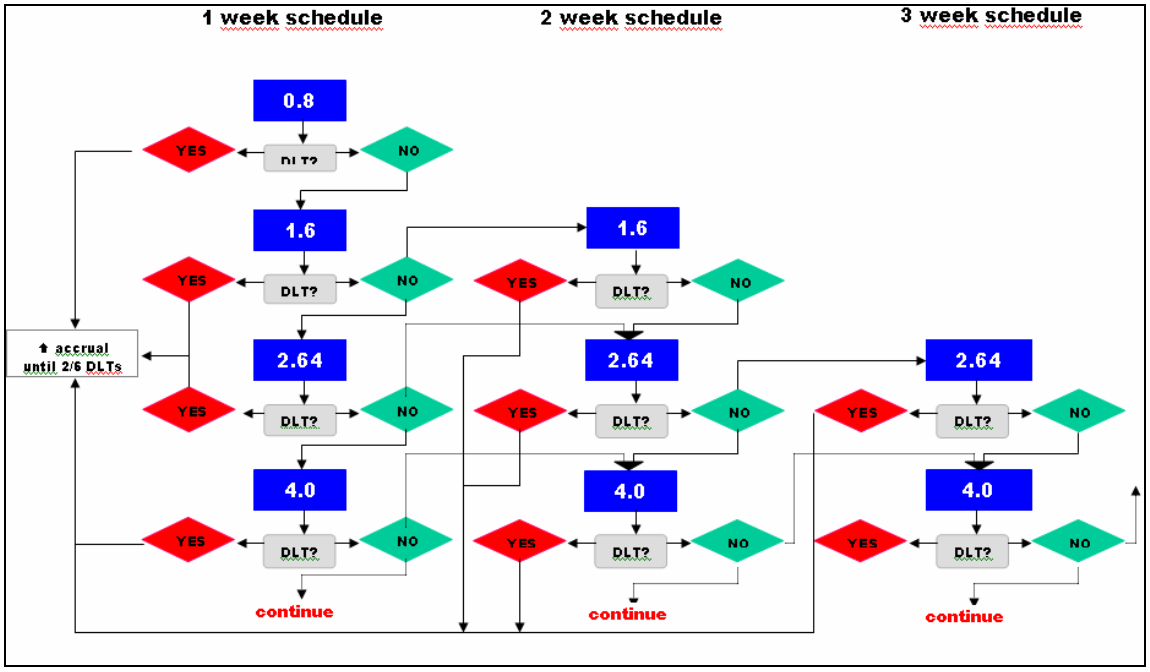


Figure 1: Complex phase I design with dose escalation within schedule

ETHICAL ISSUES IN PHASE I CLINICAL TRIALS IN ONCOLOGY

Because the risks associated with an investigational study drug are unknown, and the likelihood of therapeutic response is relatively small[4], several studies have examined the motivations of patients for participating in phase I oncology trials. Investigators conducting phase I clinical trials in oncology must adhere to the ethical norms of clinical research and therefore encounter a number of potential issues:

- maximising patient exposure to potentially therapeutic doses:
- minimizing patients treated at ineffective doses;
- minimizing patients treated at toxic doses;
- historically low probability of response in phase I trials;
- unknownn toxicity and benefit of new agent;
- difficulty in obtaining true informed consent in vulnerable patients population.

Thus, anti-cancer treatments in phase I trials are always administered with therapeutic intent, even though the main scientific objective of phase I trials is to define a suitable dose for further clinical development and define the treatment's safety profile; however, patients are always informed about the purpose of the study and of the fact that some of them could be treated at sub-therapeutic or potentially toxic doses, and they are also informed that there is a small probability that the treatment will be beneficial. There is also a small probability of a substantial and rewardiing response.

THE ISSUE OF THE ACCRUAL IN PHASE I ONCOLOGY STUDIES

Although clinical trials are a crucial step in the development of new anti-cancer treatments, their progress can be limited by slow accrual. Various researches[5,6,7] have investigated the reasons obstacling the patient accrual onto oncology studies: failure to meet eligibility criteria and patient refusal were the main reasons detected. However, due to the nature of phase I oncology study and its population, the obstacle facing recruitment into phase I trials are likely to be different than those observed in oncology trials as a whole.

In a recent work performed by Ho et al[8], where data about oncology patients seen in phase I clinic at the Princess Margaret Hospital in a five-year timeframe were analyzed, additional factors obstacling the accrual in phase I oncology studies were pointed out:

- better selection of patients;
- appropriate education of referring physicians;
- apply fewer restrictions in eligibility criteria (i.e. nr. of prior therapies).

In addition the clinical course of these end-stage patients is unpredictable, therefore the window of opportunity of starting a phase I trial may be limited. The delay involved in waiting for an appointment, being assessed in phase I clinic and then undergoing another therapy may be sufficient time for a patient's clinical status to deteriorate, thus rendering patient ineligible to enter onto the study.

MULTI-INSTITUTIONAL TRIALS

The ethical issues inherent phase I clinical trials in oncology is that a significant number of participating patients will receive 'subtherapeutic' doses. As such, a goal of phase I trials is to achieve the endpoints with the minimum number of patients necessary.

Multi-Institutional (MI) phase I trials may be favorable than single-center phase I studies to improve accrual rate, to offer a back-up plan to sponsor in case one site stops enrollment and to gain early efficacy and/or pharmacodynamic data. However, participation of several institutions may diminish the ability of clinicians to gain adeguate experiencee with the agent and to recognize its diverse cytotoxic adverse effects, thereby putting patients at risk for toxicities.

In a recent work presented at the American Society for Clinical Oncology (ASCO), Dowlati et al[1] have questioned the efficacy of MI phase I trials in achieving the goal of rapid accrual, by comparing data of single-center phase I trials versus data of MI phase I trials published from 1998 to 2005 in two main oncology scientific journals. Among the characteristcs analyzed (table 2), it emerged that MI enrolled more patients than single-center phase I trials with a greather accrual period, altough this later analysis was not statistically significant. The results of this review highlighted that the role of MI phase I trials is not clear.

The growing trend of MI phase I trial 'championed' by the pharmaceutical and biotechnology industries, have been questioned in the editorial of Tolcher et al[9]; this editorial highlight how this trend stem from mounting competitivity pressures in these industries, resulting in a quest for maximal efficiency in patient resource utilization and a strict adherence to often-unrealistic managament-driven time less. Although traditional phase I study designs have proven serviceable over the last sevaral decades, new approaches and methodologies are always welcome; however, the essential characteristics of phase I clinical trials designs should not be sacrificed in the design of new phase I clinical trials. The authors of the editorial therefore suggest phase I clinical trials conducted in one or two highly specialized sites.

PHASE I CLINICAL TRIALS IN ONCOOGY AT SENDO

SENDO is a no-profit foundation dedicated to early drug development in Oncology. It is a network of hospitals in the Southern of Europe (mainly in Italy and Switzerland) where patients for phase I and phase II clinical trials are selected and where other core research facilities are performed (for example Pharmacokinetics and Pharmacodinamics studies); the network is coordinated through an head quarter where the typical CRO functions are performed (i.e. protocol design, regulatory, monitoring, data-management and biostatistics, etc.).

Among the network of hospitals, each one audited before they can be part of the network, only a small restricted sample with proven expertise (i.e. advanced facilities for translational studies, adeguate personnel staff, etc.) can participate to first in man phase I clinical trials conducted by SENDO (no more than two or three hospitals among those enabled for each Phase I trial).

PATIENTS TRIAGE

A triage system to pre-screen records of candidates patients, such as prior therapies, laboratory results, concomitant medications, etc., may help to ensure that more potentially eligible patients are seen in the investigator site participating to the open phase I trials.

Characteristics (N=463 trials, 138 reporting accrual time)	Single-Institution	Multi-Institution
Accrual Size (p<0.0001) – Mean nr. of patients	29.0	35.6
Accrual Time (p=0.613) – Mean nr. months	22.5	25.0
	Industry	No-profit
Industry vs No-profit (p<0.05) – nr. of patients	32.8	28.4

Table 2: Single-Institution vs Multi-Institution Phase I Trials (Dowlati et al Data)

The french word 'triage' means 'picking out' (sorting) and it was used in World War I, when a 'system' was adopted for the sorting of wounded soldiers into specific groups requiring differential medical interventions according to the severity of their injuries. A similar approach (and term) is used in the hospital emergency unit, where medical or emergency personnel have to ration limited medical resources when the number of injured needing care exceeds the resources available to perform care so as to treat those patients in most need of treatment who are able to benefit first[10].

A selection system such as the one described for 'triaging' the patients, is used in a phase I clinical trial, where patients have to be selected as soon as possible so that the investigator sites can be prepared to treat a new patient and at the same time the clinical trial have a new ready-candidate for the new slots. Moreover, a good triage procedure is needed when concurrent MI phase I clinical trials are run at the same centres.

MATERIAL AND METHODS

Because of the issues discussed in the previous sections, coordinating phaseI I clinical trials in oncology requires a continuos and prompt review of patients status (toxic effects due to study therapy), so that DLT can be detected soon and decisions affecting the course of the study, such as opening or closing a new cohort, can be taken as soon as possible. To achieve this goal, an early identification of cadidates to be enrolled for the next available slot in the study must be done, otherwise there is the risk to delay/interrupt the course of the study. Usually, and for many years at SENDO, the management of patients triage is manually managed with continuos phone-conferences between study Project Manager (PM) and the Clinical Coordinator (CC) of the study, together with documentation, usually excel file, documenting the study status (opened cohorts, slots available, patients waiting to be enrolled, etc.). Moreover, investigators have to continuosly consult the study PM to communicate potential candidates and check if there is a slot available in any of the studies onto which the Investigator is participating (or when, potentially, the next slot wille be available).

The lack of an electronic system helping the study PM, the CC and the Investigators make the patients triage something difficult to manage. For this reasons we developed a web based application, web-triage, for managing the patients triage allowing anyone involved in the study to share information about study status and to propose autonomously patient candidates.

SYSTEM DESIGN

Web-Triage was developed using the ASP.NET web development framework. ASP.NET is a unified Web development model that includes the services necessary to build enterprise-class Web applications.

ASP.NET is part of the .NET Framework, so when coding ASP.NET applications there is access to all the classes of the .NET Framework. Applications can be coded in any language compatible with the common language runtime (CLR), including Microsoft Visual Basic, C#, JavaScript .NET, and J#. These languages enable the development of ASP.NET applications that benefit from the common language runtime (CLR), type safety, inheritance, and so on.

N-TIER SYSTEM

N-tier architecture is a client-server model where each part, the user-interface, business rules, data access and data storage, are developed as separate modules. Thus each module can be updated or replaced if requirements change. Often modules will be on separate platforms (i.e. web server, database server). A conceptual overview is given in figure 2.

The data layer is split into two separate layers. The first consists of the set of stored procedures implemented directly within the database. These stored procedures run on the server and provide basic data only. Not only are they pre-compiled and pre-optimized, but they are also tested separately and, in the case of SQL Server, run within the Query Analyzer to make sure that there is not inefficient table scan.

The next layer consists of a set of classes which call and handle the stored procedures. You will need one class per group of stored procedures which will handle all Select, Insert, Update, and Delete operations on the database. These classes handle all requests to or from the actual database and provide a shield to application data. All requests must pass through this layer and all concurrency issues can and must be handled here. This ensures data integrity is

maintained and that no other source can modify the data in any way.

If for any reason a modification of the database structures is required, the data layer can be easily modified without affecting any other layers. This considerably simplifies the maintenance of the application.

The business rule layer is implemented in order to encapsulate the business rules. This has classes which implement business functionality. They neither access data directly (except through the data layer), nor are they involved with the display or presentation of data to the user. All we are interested of at this point are the complexities of the business itself. By isolating this functionality, we are able to concentrate on the guts of our system without the worry of the design, workflow, or database access and related concurrent problems. If the business changes, only the business layer is affected, again considerably simplifying future maintenance and/or enhancements.

The workflow layer is one of the optional layers and it deals with data flow to and from the system. It may or may not interact directly with the user interface, but it always deals with external data sources.

The presentation layer handles everything to do with the presentation of the system. This does not just include web forms (user interface), but also all the classes which will help you in presenting the data (reports).

SYSTEM SECURITY

The Web Triage server is hosted in a dedicated rack of a high-restricted, access-controlled data center. Only authorized people can access it for maintenance operations. Communication among Internet clients and the application is HTTPS-encoded and a suitably configured firewall is placed in-between. Data are stored in a SQL Server relational database, where, they cab be easily encrypted.

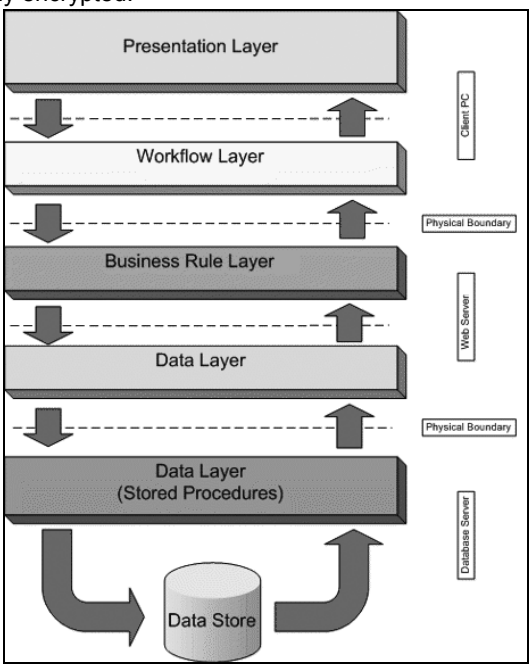


Figure 2: N-Tier conceptual overview

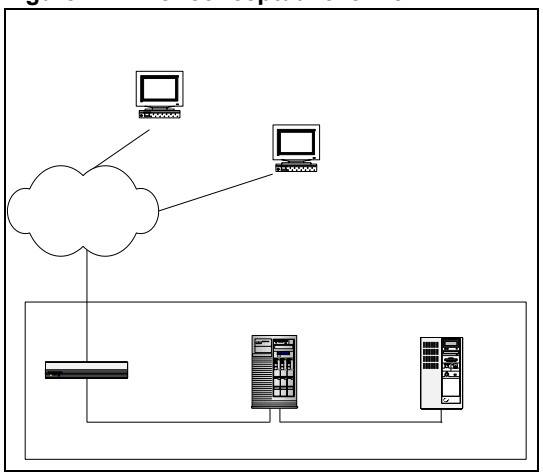


Figure 3: Simplified schema of Web-Triage network architecture

TAKE A TOUR IN THE WEB-TRIAGE APPLICATION

DEFINE A STUDY

The first step in the usage of the web-triage is the set-up of the study. This action is performed at the SENDO data-center by the web-triage administrator together with the assigned study PM.

SETTING THE DOSE-LEVELS

Here the expected (by-protocol) dose-levels are defined (figure 4), with dose information and initial slot dimension.

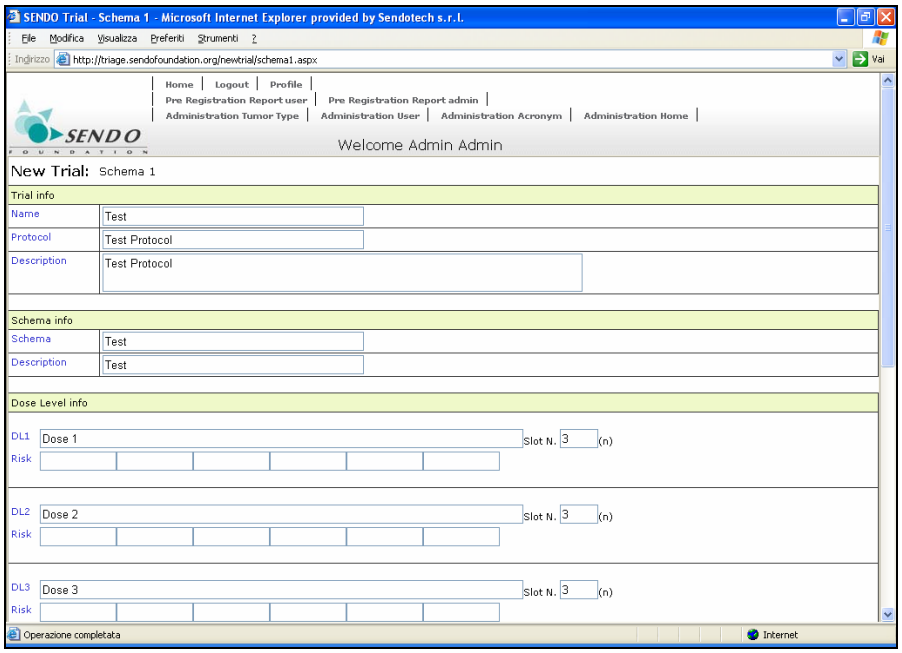


Figure 4: Setting the study planned dose levels

SETTING THE DATA TO BE COLLECTED

Variables to be collected on registration form are set-up. Usually, the eligibility checklist together with main data to confirm the patient is eligible to enter onto the study are collected: demographics, prior therapies, hematology and chemistry tests, are the main information required.

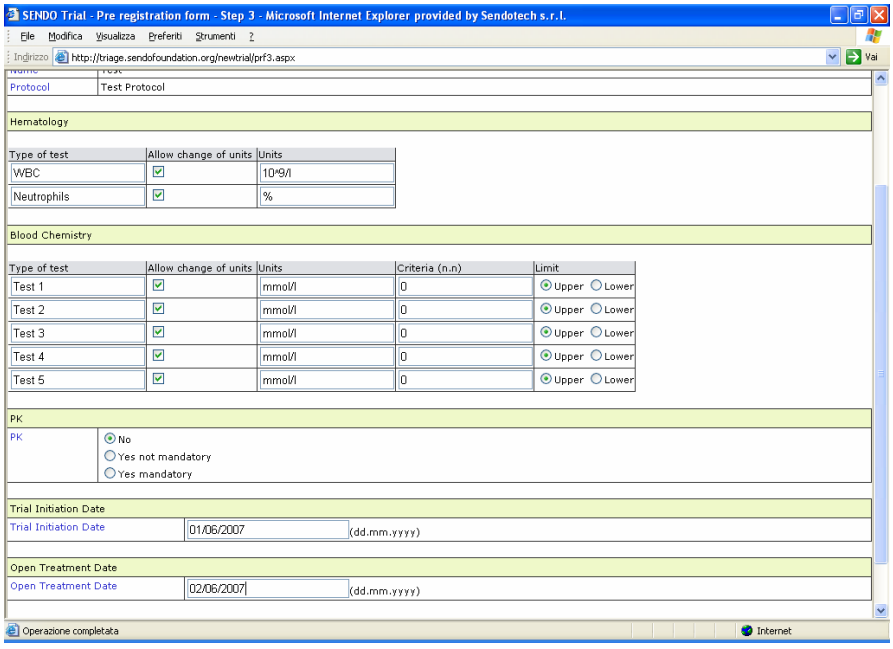


Figure 5: Information to be collected

LOG-IN TO THE APPLICATION FROM THE INVESTIGATOR SITE

The system can be accessed through a web page at the SENDO Foundation, where the list of open trial at SENDO managed through the web triage are shown (figure 6). Each user at the data centre SENDO and each Investigator participating to the SENDO open trials, is assigned a username with a personal password. Once the user logged-in onto the system, a table showing the opened trials onto which the user is enabled to enroll patients is shown (figure 7).

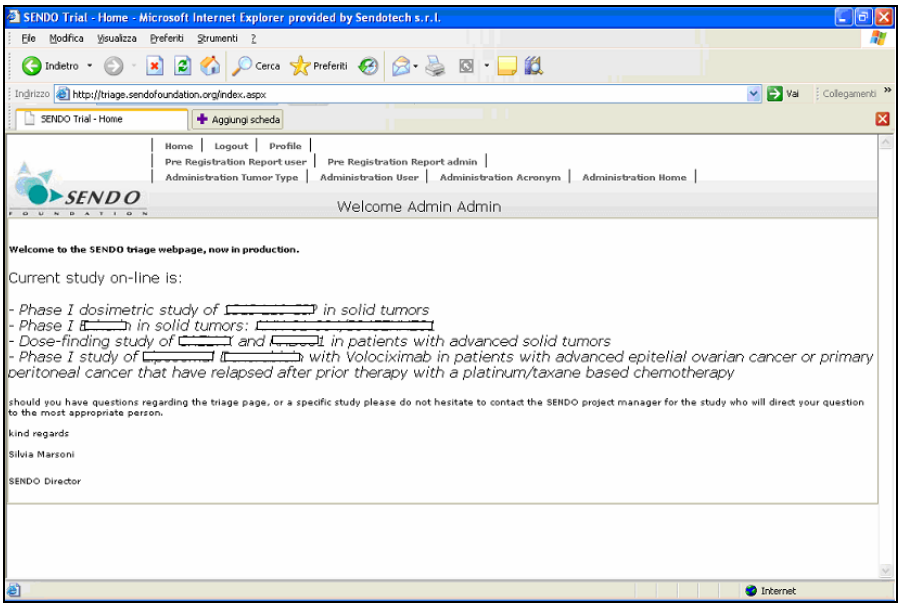
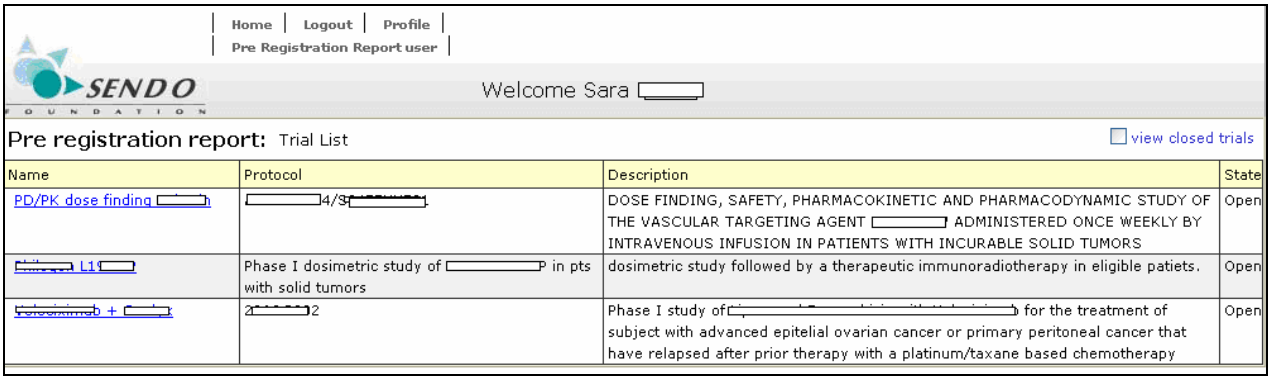


Figure 6: Web-Triage Welcome Page



Name	Protocol	Description	State
PD/PK dose finding [redacted]	[redacted]	DOSE FINDING, SAFETY, PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF THE VASCULAR TARGETING AGENT [redacted] ADMINISTERED ONCE WEEKLY BY INTRAVENOUS INFUSION IN PATIENTS WITH INCURABLE SOLID TUMORS	Open
[redacted] L1[redacted]	Phase I dosimetric study of [redacted] in pts with solid tumors	dosimetric study followed by a therapeutic immunoradiotherapy in eligible patiets.	Open
[redacted] + [redacted]	[redacted]	Phase I study of [redacted] for the treatment of subject with advanced epitelial ovarian cancer or primary peritoneal cancer that have relapsed after prior therapy with a platinum/taxane based chemotherapy	Open

Figure 7: List of open trials

PROPOSING A CANDIDATE

Once the investigator has selected the trial, the status is shown (figure 8) and information about study cohorts (opened dose levels) are shown. In the example showed in figure 8, the first dose level (7.5 + 40) was closed because no DLT criteria for stopping the dose-escalation were found. “15+40” is the current opened dose level and where the investigator can ‘Add a Patient’. Morever, the system shows the first theoretical date, EPTD (Early Planned Treatment Date), if no delay in the treatment course of previous patients, onto which the next patient can be enrolled (in the example it is the 24th september 2007):

When the investigator select the ‘Add a Patient’ option, the information to be collected are prompted to the investigator (figure 9). The system has an internal engine for simple data-entry checks (see error shown in figure 9) and facilities to select data-entry item from a pre-defined list (see list of active principles for chemotherapy in figure 9).

Finaly, when all information about the patient canidate are correctly entered, a notification is sent to the study PM (figure 10). At this stage the investigator was able to see the study status and to plan the enrollment of the patient onto the study indipendently.

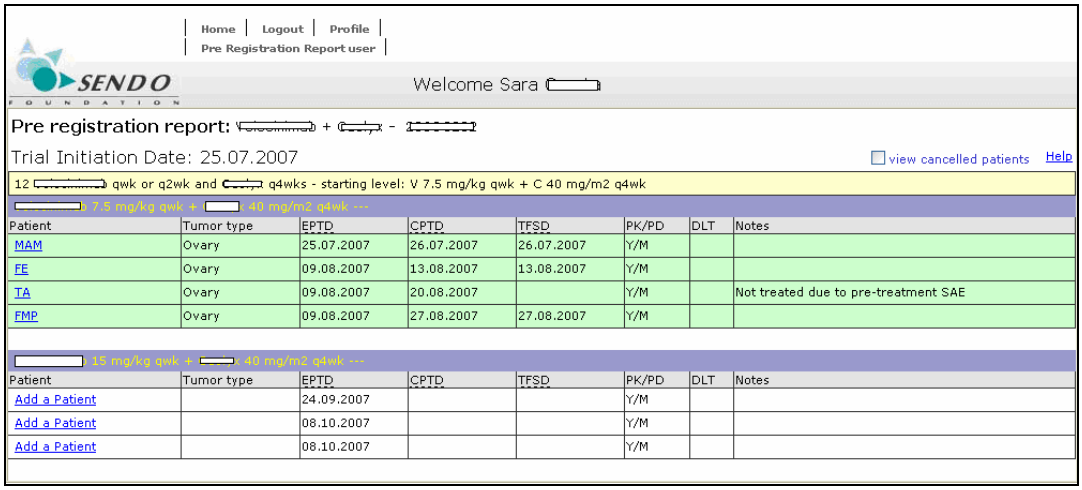


Figure 8: List of open trials

REVIEWING PATIENT CANDIDATES

As soon as the study PM receives the email notification, it reviews the information provided and decides to either 'accept', 'review or accept with restriction' or 'reject' the proposed candidate (the traffic lights in figure 10). Note that the decision take onto consideration also the study status (enrolled patients currently on-treatment).

If the patient candidate is suitable for study enrollment, the study PM assigns an initial flag (pre-registration status) to the patient. By doing this, the investigator, but also all other participants, is aware that the slot is potentially assigned. Once the investigator is alerted that his candidate was accepted, the registration onto the study can be formalised; if in the meanwhile the candidate is not anymore available (i.e. change in patient condition) and the slot can be made available to other potential patient candidates.

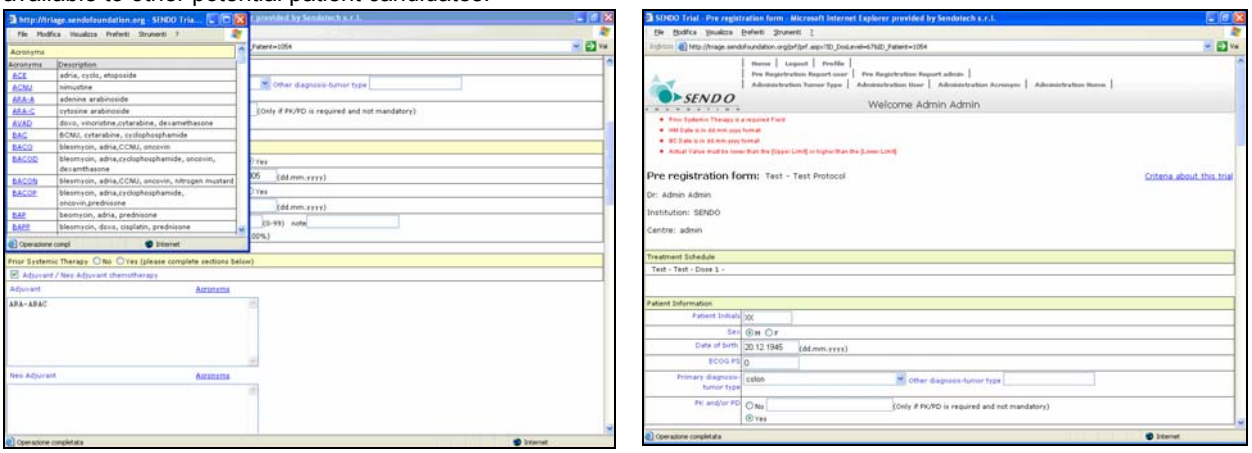


Figure 9: Patient Candidates Data-Entry

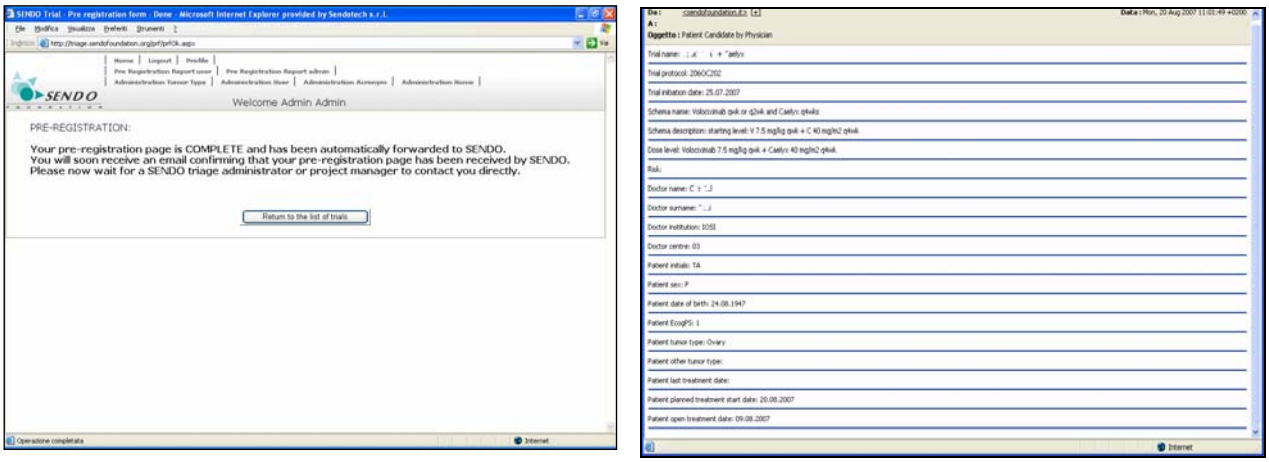


Figure 10: A Candidate is proposed and a notification is e-mailed to the study PM

CLOSING/OPENING A DOSE-LEVEL

As soon as a step in the study is completed, a dose-level can be closed so that the Investigator are not allowed anymore to candidate patient for that level and the next planned dose can be opened.

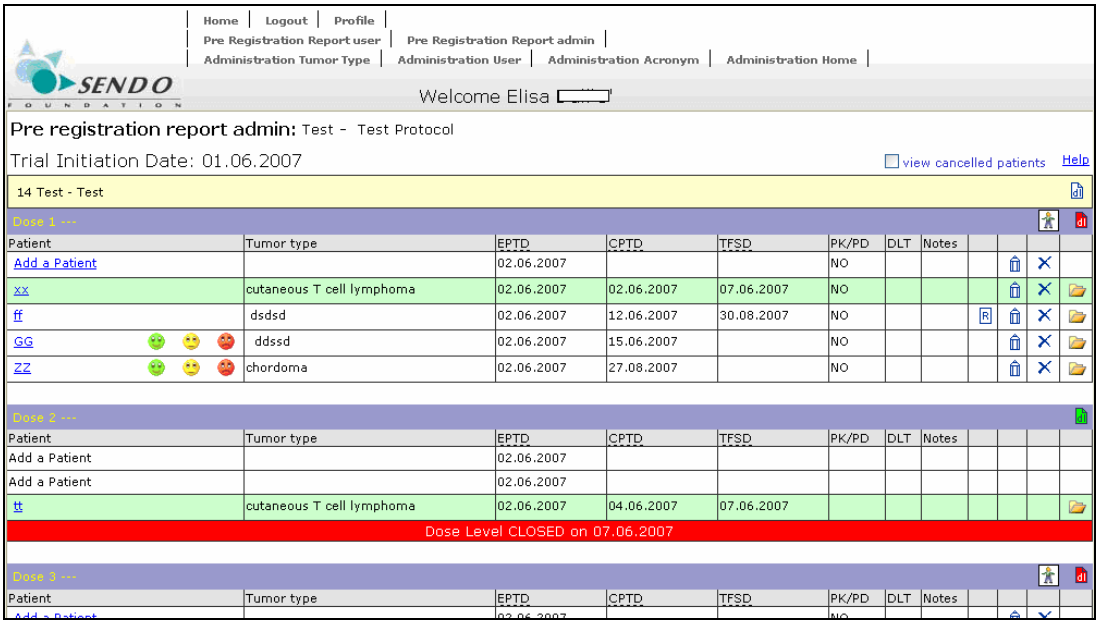


Figure 11: The study status showed to the study PM

FUTURE DEVELOPMENT

The Web-Triage application is a tool to facilitate the management of slot allocation and it replaces an activity that before at SENDO, but probably still in other organizations performing phase I study, was managed trough an excel file shared between the PM and the CC of the study. After the approval for the enrolment of new patient at SENDO coordinating center by the Project Manager, the formal registration of the patient onto the study is still managed through paper form, signed and dated. Therefore the official information confirming the approval of patient registration onto the study is on paper and patient data collected through paper CRF and/or validated electronic clinical database. Thus, although for this reason we think a proper system validation approach was not necessary, it is our plan to re-consider the validation activities in view of eliminating the paper form and eventually integrate data collected through this application with other applications used for collecting data of patient enrolled onto the study.

CONCLUSIONS

At the time of molecular medicine translational Phase 1 trials are crucial for the successful development of new anticancer drugs while offering the utmost potential for therapeutic benefit to patients. Translation trials are often MI given that rarely a single cancer center has all the required medical and research facilities for its conduction and because of the restrictive timeframes requested by drug companies. The seamless and timing organization of a MI translational trial is a complex logistic undertaking which on top and foremost must avoid exposing patients to undue risk while offering at least a potential therapeutic benefit. Timely patient allocation is a key feature to translational studies. The Web-Triage can be a useful time and resource sparing tool for trial slot assignment for both trial investigators and trial coordinator, in addition increasing eligibility compliance and the potential fort re-routing patients to alternative trials/treatments in the shortest possible time.

REFERENCES

1. Dowlati A., Manda S., Patrick L., Remick S, Gibbons J., Fu P. Multi-institutional phase I trials involve more patients and longer accrual time compared to single institution trials. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I Vol. 25, No. 18S (June 20 Supplement), 2007: 2500
2. Parmanand Singh. Acharya Hemachandra and the (so called) Fibonacci Numbers. Math. Ed. Siwan. 1986: 20(1):28-30.
3. Simon R. Clinical Trials in Cancer. Section 1: Design and Analysis of Clinical Trials. In DeVita T, Hellman S, Rosenberg S. Cancer: Principles and Practice of Oncology, Fifth Edition. Chapter 20.1 513-514
4. Agrawal M, Emanuel E. Ethics of phase I oncology trials: re-examining the arguments and data. JAMA 2003; 290: 1075-82
5. Risks and benefits of phase I oncology trials, 1991 through 2002. N Engl J Med 2005; 352:895-904

6. Rate limiting factors in recruitment of patients to clinical trials in cancer: descriptive study. BMJ 2003; 327:320-1
7. Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrolment. J Clin Oncol 2001; 19:1728-33
8. Ho J, Pond G, Newman C, Maclean M, Chen E, Oza A, Siu L. Barriers in phase I cancer clinical trials referrals and enrollment: five-year experience at the Princess Maragaret Hospital. BMC Cancer 2006; 6:263
9. Tolcher A, Takimoto C, Rowinsky E. The multifocal, multi-institutional, and sometimes even global phase I study: a better life for phase I evaluations or just 'living large'. J Clin Oncol 2002; 20: 4276-4278
10. Wikipedia – The free encyclopedia. www.wikipedia.com

RECCOMENDED READING

For more details on technologies used, check the below web resources:

- **HTTP://MSDN2.MICROSOFT.COM/EN-US/LIBRARY/MS973279.ASPX**
- **HTTP://WWW.MICROSOFT.COM/BELUX/MSDN/NL/COMMUNITY/COLUMNS/HYATT/NTIER1.MSPX**
- **HTTP://MSDN2.MICROSOFT.COM/IT-IT/NETFRAMEWORK/DEFAULT.ASPX**
- **HTTP://WWW.WEBOPEDIA.COM/QUICK_REF/APP.ARCH.ASP**

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Angelo Tinazzi
SENDO Tech S.r.l.
Via Visconti di Modrone 12
Milan / 20122
Work Phone: 0039 02 76420426 Fax: 0039 02 76017484
Email: tinazzia@sendo-org.it Web: http://www.sendofoundation.org
Eventi Telematici website: http://www.evtel.it