PhUSE 2007

Paper AD03

LSLV to Final Clinical Study Report Tables in 24 hours, Dream or Reality?

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ABSTRACT

Reality! The production of final clinical study report tables in 24 hours from Last Subject Last Visit (LSLV) is a reality for Phase I healthy volunteer studies in Pfizer. Today, the majority of studies performed at any one of Pfizer's four Clinical Research Units globally will have final tables issued within 24 hours. This is no longer a challenge for Pfizer but is standard practice.

This paper focuses on the technology, standardisation and processes involved in enabling 24 hour reporting to be a reality, including an overview of the changes required to Pfizer systems, and the challenges faced.

INTRODUCTION

In 2006 the global head of the Clinical Research Operations group in Pfizer set a challenging goal to the company: to issue final clinical study report presentations, within 24 hours of the last subject last visit date, for a study run at one of Pfizer's Clinical Research Units. This aptly became known as the "24 hour goal" within Pfizer.

In reality the "24 hour goal" is separated into two goals. Firstly the Clinical Research Units lock the clinical study database within 24 hours of the last subject last visit. Then the clinical programmers issue final clinical study report presentations within 24 hour of database lock. In essence the whole process from last subject last visit to final clinical study report tables should take just 48 hours, an extremely challenging goal!

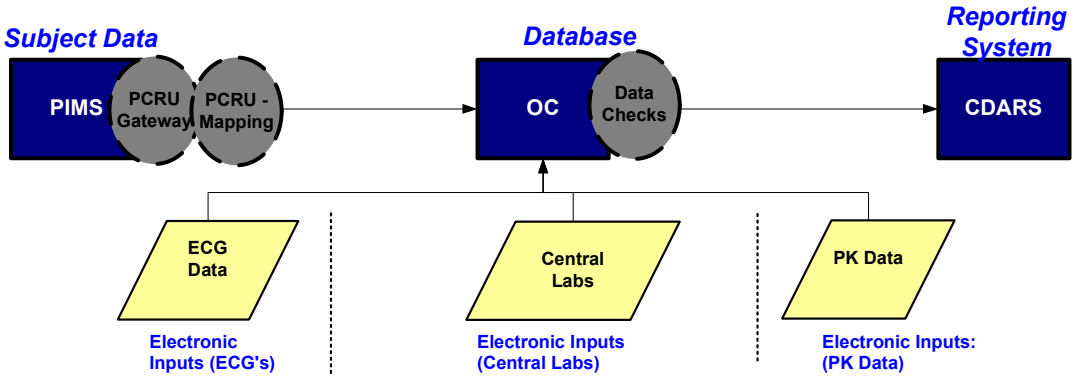
A team (the Systems Governance Team (SGT)) was already in existence, to examine the potential enhancements to systems used at the Clinical Research Units. The "24 hour goal" was appropriately assigned to the SGT team to investigate what additional changes were required to the systems and processes for Phase 1 studies to enable faster and more efficient reporting of clinical trial data. There were two immediate and fundamental changes required at Pfizer; to completely alter the approach to the reporting of phase 1 clinical studies by ensuring most programming activities were completed up front, in advance of last subject last visit, hence resulting in fewer tasks to be completed at the later stages of the process. Secondly, to reduce the hand-offs between team members and functional lines.

TECHNOLOGY

The Pfizer Clinical Research Units (PCRUs) use the Phase 1 Management System for the electronic management of the data for all Phase 1 studies. The Phase 1 Management System (more commonly referred to as PIMS) is developed by RM Systems, based in Illinois, USA. Pfizer still continues to work closely with RM Systems in further developing PIMS to meet Pfizer standards and goals, and ensure efficient data management at the Clinical Research Units.

PIMS is not just a data collection tool; it is also used by the PCRUs in the coordination of volunteer recruitment, management of the Phase 1 trials, as well as instant electronic data collection. As there is an electronic data capture tool within the PIMS system, no paper CRFs are used in any studies performed at the Clinical Research Units.

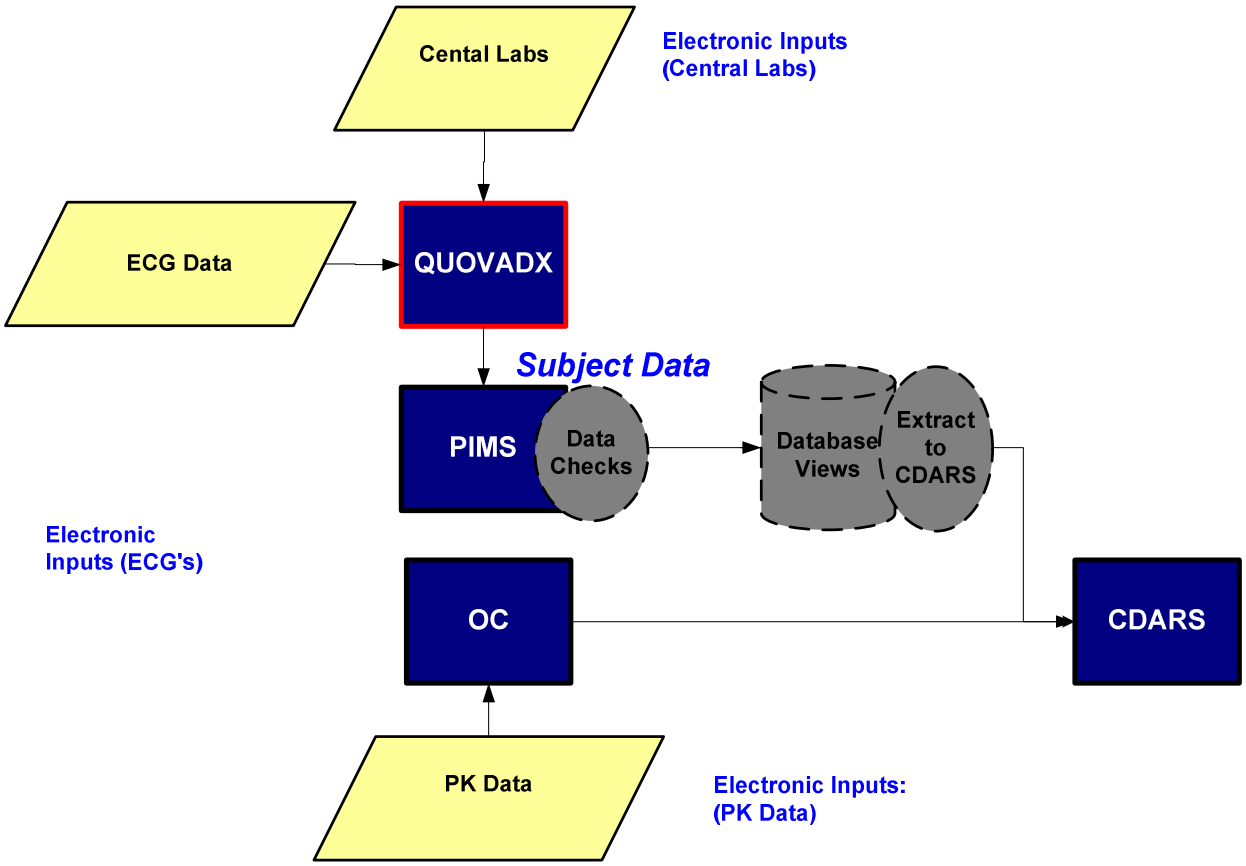
Previously, data captured in PIMS was electronically transferred and loaded onto the in-house Oracle Clinical (OC) database. Only then could it be extracted and reported through the in-house reporting system (Clinical Data Analysis & Reporting System, CDARS):



Electronic Inputs (Out of Unit)

The resulting timelines for database lock and reporting were reliant on data handoffs between PIMS, OC, an in-house data management team and finally the clinical programmer.

Recent updates to PIMS have enabled data to be extracted directly from PIMS using the in-house reporting system CDARS, hence by-passing OC: data collected at the clinic is automatically entered into the PIMS windows, and extracted and reported directly out of CDARS:



There is no longer a need to have two databases maintaining the same data, and there is no longer a need to perform discrepancy management between the PIMS and OC databases. The focus has shifted to the Clinical Research Unit staff to clean and manage the data and database, ensuring a more efficient and reliable process, and removing the reliance on OC data management activities.

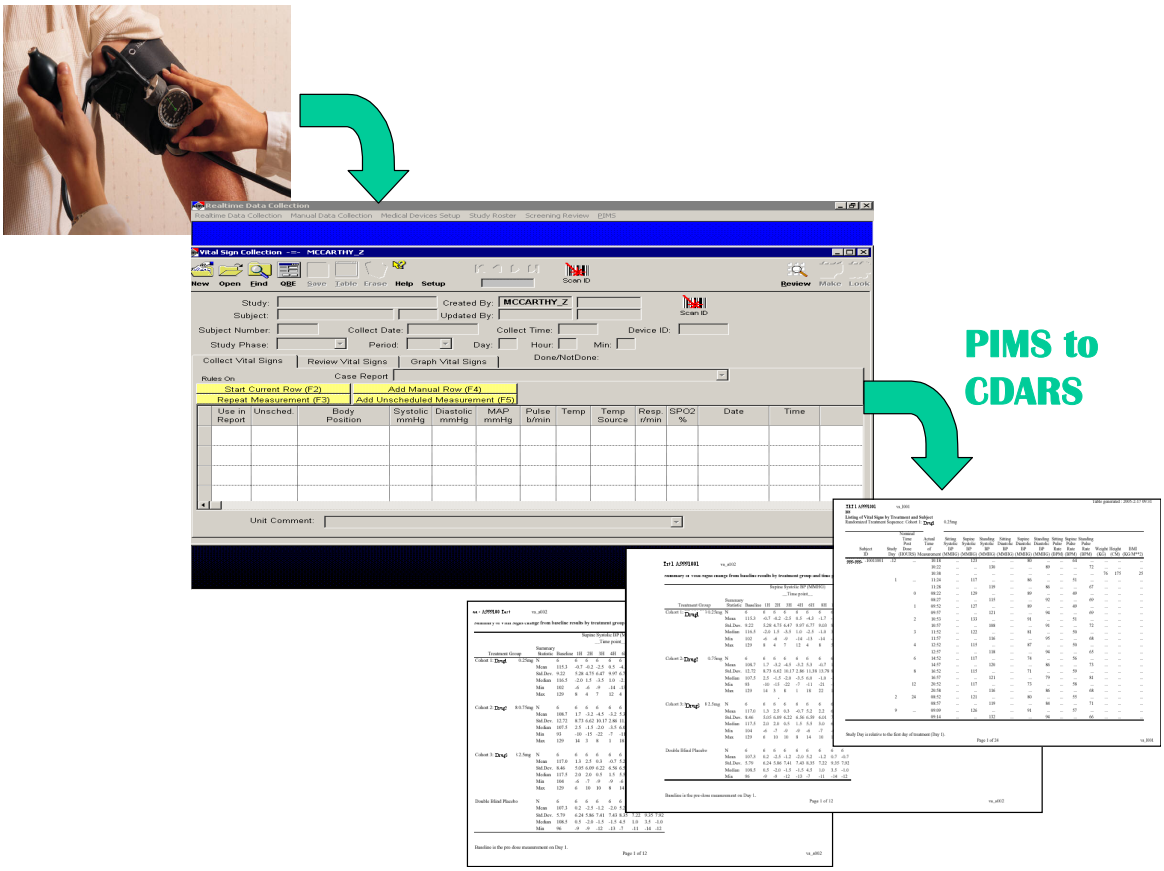
With the availability of data directly from PIMS to the reporting system, the “24 hour goal” moved closer towards reality.

REAL TIME ACCESS TO THE DATA

Fast and efficient access to the data was instrumental to the whole "24 hour goal" process. Early access to the clinical study data, during the study conduct phase, would enable the clinical study report presentations to be set up in advance of the database lock. This in itself would reduce post database lock reporting timelines. It would also enable programming of any efficacy endpoints to commence as soon as efficacy data was available in PIMS.

To facilitate this, real time access to the PIMS database was made available to the clinical programmers by the use of materialised views. Materialised views take a snapshot of the data in a database at a particular time point. In PIMS, the views are refreshed every 24 hours, allowing a snapshot of the clinical study data every 24 hours. Materialised views introduce some efficiency into the data access process particularly where the views are accessing numerous data tables for each view.

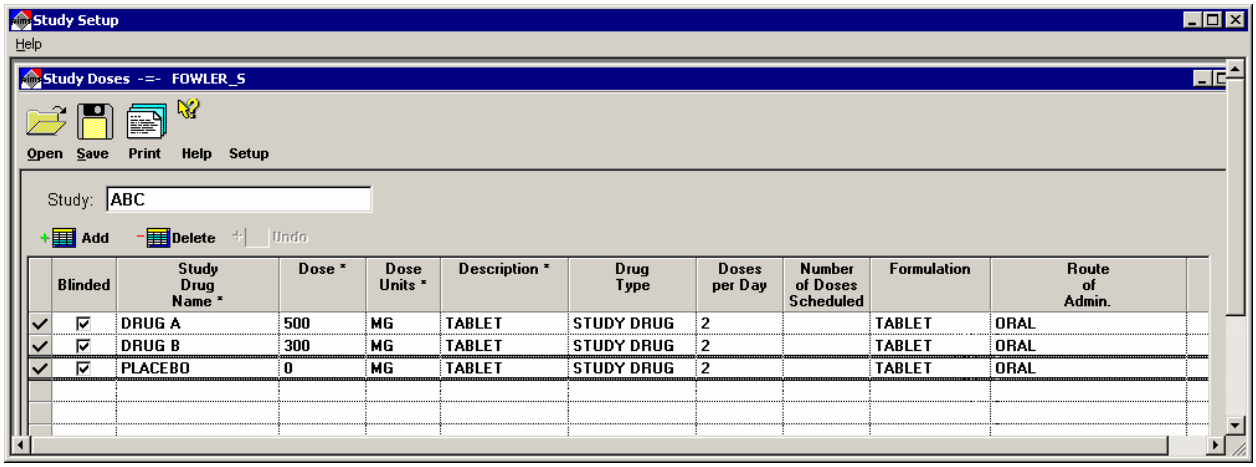
Implementation of materialised views in PIMS gave the programmers access to the PIMS data 24 hours after data was entered into the PIMS windows. However, for some of the key data types access is immediate, and the programmers can access the data as soon as it is entered into PIMS. As a subject attends a visit at the Clinical Research Unit, the data is entered directly into the relevant PIMS window and is available to the programmer the very next day:



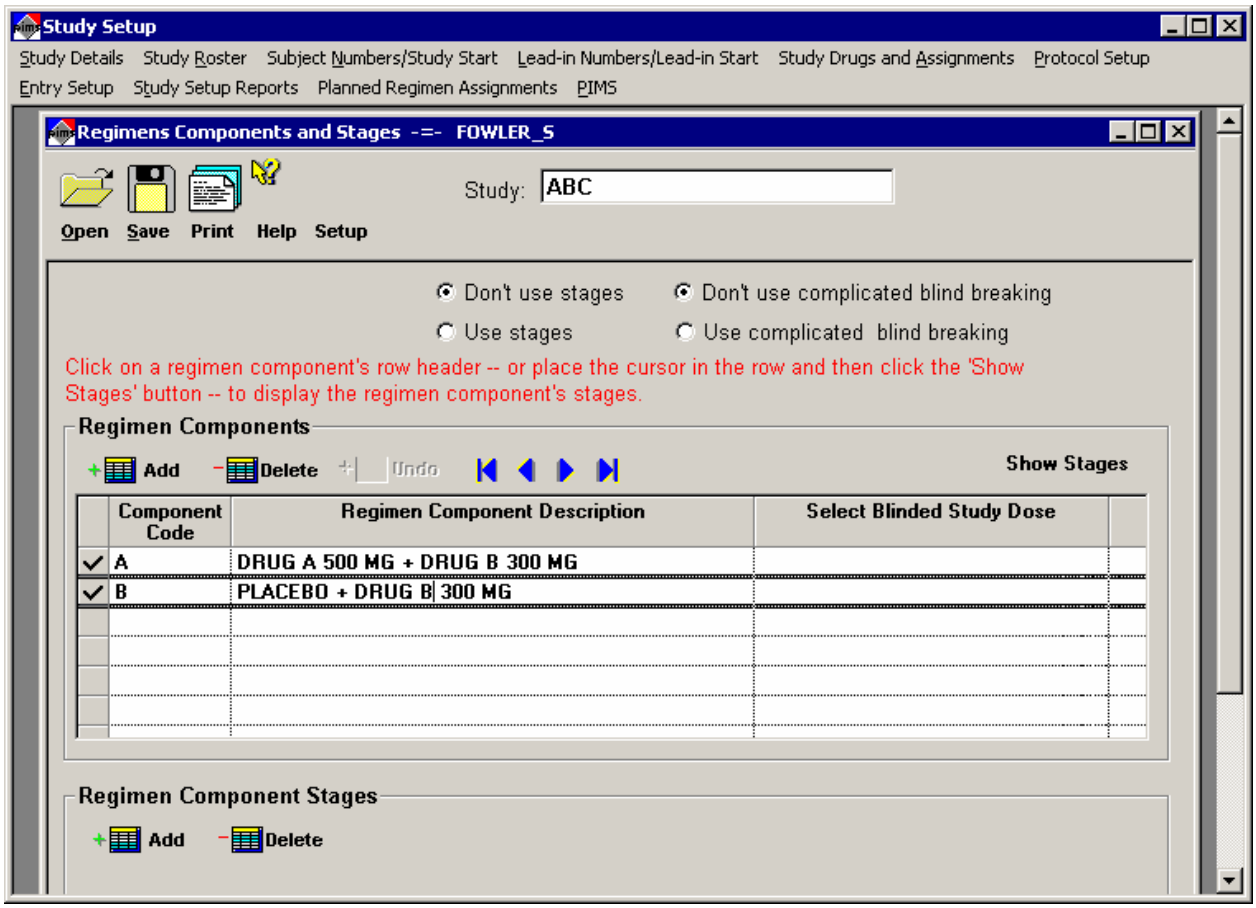
TREATMENT AND RANDOMISATION INFORMATION

Historically, the randomisation information for all Pfizer studies was stored and extracted from the in-house Oracle Clinical database. So despite the availability of the actual dosing level information for each subject from within PIMS, the randomisation and planned treatment information was still extracted from OC. To move away from the reliance of data in OC, the PIMS windows were updated to enable the Pharmacist at the Clinical Research Unit to load the subject randomisation information directly in to PIMS at study setup. Functionality was also added to enable them to break the study blind within the PIMS system. The actual randomisation still occurs in OC, but by transferring the information into PIMS ensures all treatment data for the study is available and extracted from one system, and datamanagement support is no long required for this data component in OC.

There are two key windows in PIMS storing the treatment level information: the study doses window, which lists the dosing information for the study drug:



And the Regimen components window which lists the study sequences/periods/cohort level information:

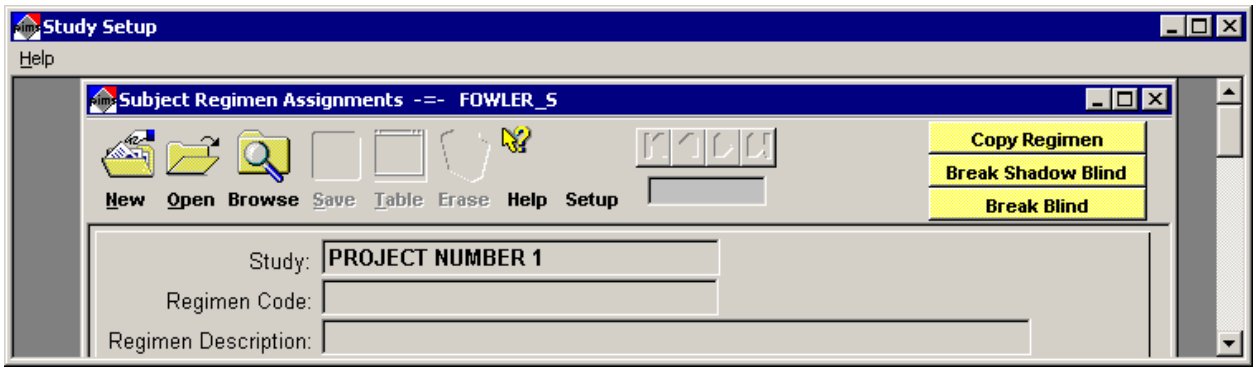


The Pharmacist is the only person at the Clinical Research Unit that has the authority to link subjects to their treatment regimen, no one else has access to the window that stores this information. This ensures all the Clinical Research Unit staff and Sponsor are blinded to this data.

Data from both windows feeds into two separate views: the treatment view links subjects to their planned and actual treatments; the dosing view provides detailed information on the individual subject dosing records. Both views are unblinded at database lock once the study has been unblinded in PIMS. However, for sponsor open studies (where

the investigator and subject are blind, but the sponsor is open), functionality was required to enable the blind to be broken during study conduct to just the clinical programmers, while still ensuring the PCRU and study team remained blind. This would enable the programmers to produce the clinical study report presentations upfront using the actual treatment records on a subset of data, as soon as data is available in PIMS.

As a result, the concept of the "Shadow break blind" was developed for sponsor open studies. This allows the pharmacist to break the blind to just the programmers, whilst ensuring everyone else remains blind. Two additional views, the shadow views, were developed. These shadow views mimic the treatment and dosing views mentioned above. Access to these is only available to the programmers. A process was developed which allows the pharmacist to press the "Break Shadow Blind" button, on request from the study statistician, during study conduct:



This unblinds the two shadow views, enabling just the programmer to gain access to the actual treatment and dosing information, whilst the treatment and dosing views remain blind.

DATA MANAGEMENT ACTIVITIES

Having moved away from data loading into OC, all data management activities moved to within the Clinical Research Units. ECG, Vitals and Laboratory data is loaded automatically into PIMS directly from the source, so there are no transcription errors in these data types. However, for other data types, the PCRUs needed to ensure the data was clean within PIMS before database release. To facilitate this, data quality specifications were written into the PIMS system, these ensure any out of scope values entered erroneously into PIMS are flagged at the point of entry. The PCRUs also guarantee real time cleaning of the data on an ongoing basis; this avoids a bolus of work at the end of the study and facilitates up front table production by the programmers.

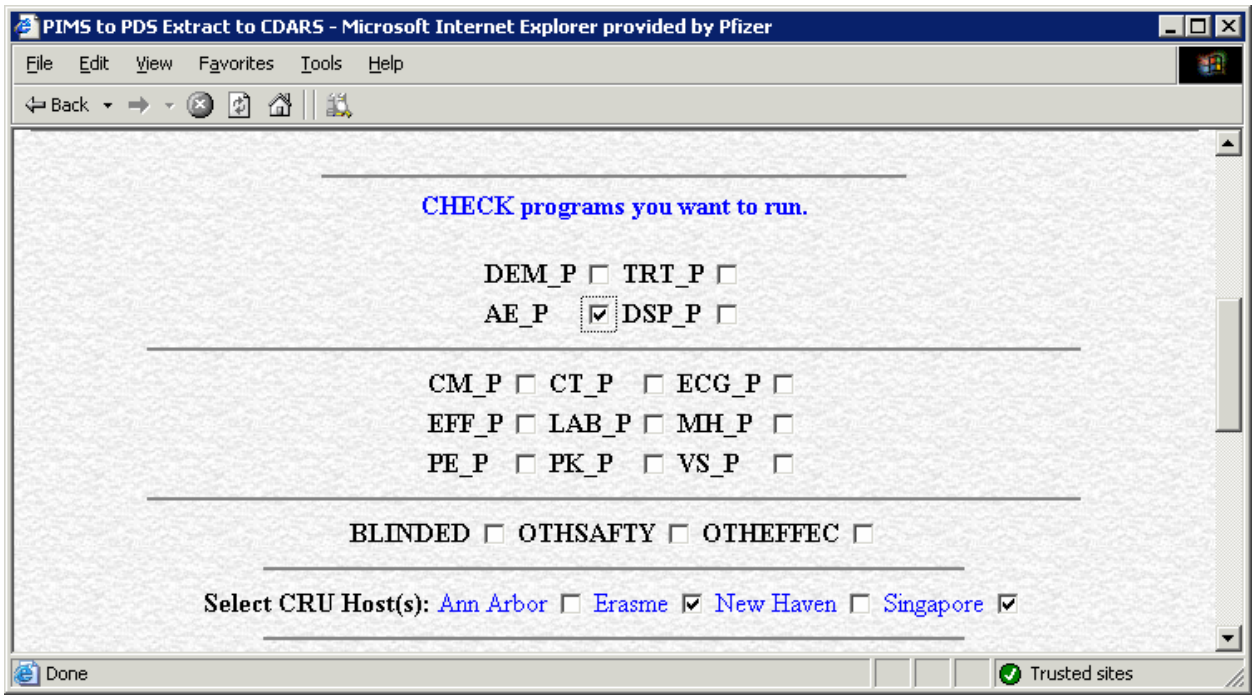
WHO drug coding information and MedRA coding is now incorporated within PIMS. The dictionary within PIMS is linked to the Pfizer global dictionaries on the Oracle Clinical database. The PIMS dictionaries are refreshed every 24 hours, ensuring any updates to the Pfizer dictionaries are automatically incorporated within PIMS. If there are any terms in the PIMS database for which there is no code available, then this is automatically picked up by PIMS and sent to the dictionary group to code. Once they have updated the OC dictionaries, PIMS will pick this up in its nightly refresh. A similar process is available to ensure the laboratory tests are also coded within PIMS.

The SGT team have devised a PIMS query system. Any queries raised on the PIMS data are documented, and communicated through this process, and not by email flow between individuals. This is a global process and has facilitated the fast and efficient management of PIMS data queries.

A database lock process has been developed specifically for studies conducted in PIMS to correspond to the Pfizer standard operating procedures. At the end of a clinical trial, it is the responsibility of the Clinical Research Unit to adhere to the final study unblinding and database lock processes within PIMS and to inform the study team.

ENHANCEMENTS TO THE EXTRACTION CODE

In addition to changes at the Clinical Research Units, enhancements were also required to the in-house reporting system, CDARS. Firstly, the CDARS extraction code was updated to enable extraction directly from the PIMS system or from OC, depending on the study database. In line with this, the CDARS interface was enhanced to enable the user to select at which PCRU the study was conducted, essentially which PIMS database to access. This functionality was further enhanced to enable more than one PCRU to be selected to allow for multi-centre studies, where a study is conducted at more than one PCRU:



For multi-centre PIMS studies, the SAS® extraction code automatically merges the data types from the selected PCRUs into one extracted dataset per data type, ie in the above example, the adverse events data is extracted from the Erasme and Singapore PIMS databases and merged together resulting in one adverse event extracted dataset for the programmers.

With the availability of the shadow treatment views, further enhancements were made to the treatment extract code, which now checks whether the PIMS database is locked to determine which treatment views to access. If the PIMS database is locked, then the treatment extract code extracts data from the treatment views. However, if the PIMS database is not locked, then the data is extracted from the shadow treatment views. In both situations a warning is flagged in the SAS log file which documents which treatment views have been used.

STANDARDISATION

The global standardization of data, systems and processes was instrumental to the success of the “24 hour goal”. This would ensure fast and efficient data capture and facilitate the production of final data presentations.

There are four Clinical Research Units in Pfizer, in three different countries; all were using different versions of PIMS, different technologies were used within each clinic, and all were working to different standards. In essence they were four stand alone clinics. The initial challenge was to ensure all the Clinical Research Units globally worked to the same standards, using the same version of PIMS, using the same technology and ensure working practices at all the Units were identical. In parallel, similar issues were also addressed within the clinical programming group globally. Ensuring processes and software to report phase 1 studies by clinical programmers were identical at all the Pfizer sites.

THE ROLE OF THE SYSTEMS GOVERNANCE TEAM

The Systems Governance Team (SGT) was established to pursue the philosophy of “one global system, one global process” across all functional lines. The team consists of designated members from each Clinical research Unit, a clinical programmer from each site, members from the PIMS development team, PIMS system project manager and a group head to lead the team: a total of 12 team members, each representing the global functional lines required to achieve the “24 hour goal”. The success of this team is guaranteed by the empowerment of each team member to make decisions on behalf of their functional line; this has ensured, and continues to ensure, fast efficient decisions within the weekly meetings.

Most importantly, the launch of the SGT team has established excellent lines of communication between colleagues:

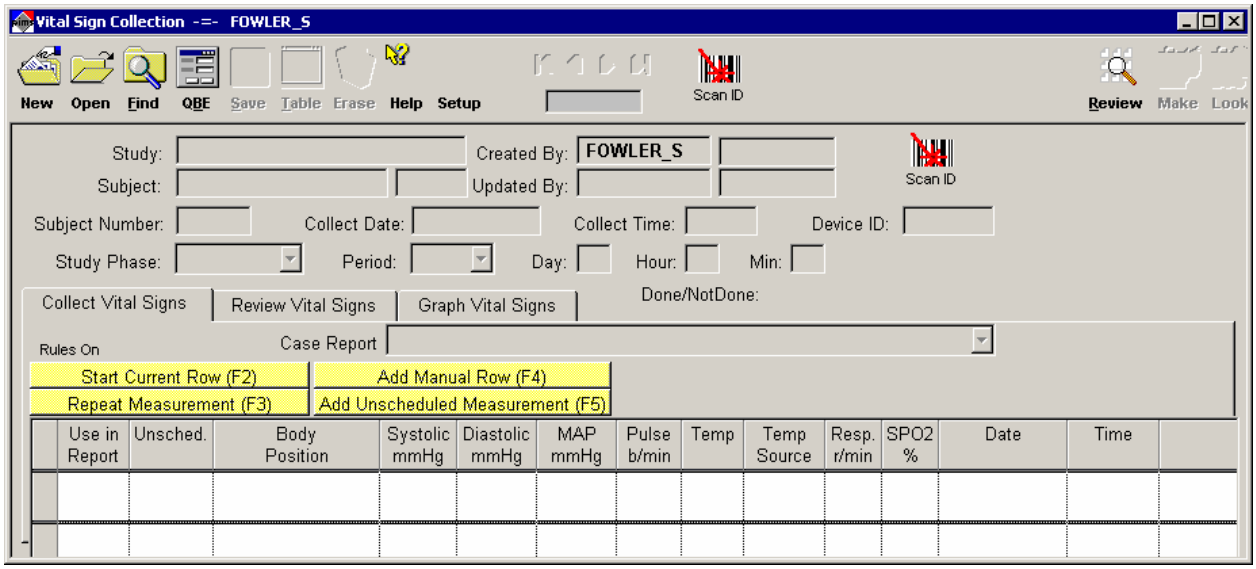
- Between global PCRU members from each of the clinical research units, to discuss best global working practices. This has encouraged globalization and standardization across the different PCRUs. They now run as one clinical research unit in four global sites. This has enabled multi-centre studies to be run efficiently across the different PCRUs.

- Clinical programmers producing the end presentations have direct contact with their Clinical Research Unit colleagues who collect and manage the raw data. This has encouraged open discussions on how best to collect and database the data to facilitate reporting activities.
- Direct contact between the PIMS developers, the clinical programmers and the PCRUs has ensured any enhancements to the PIMS system have minimal impact to the reporting system.

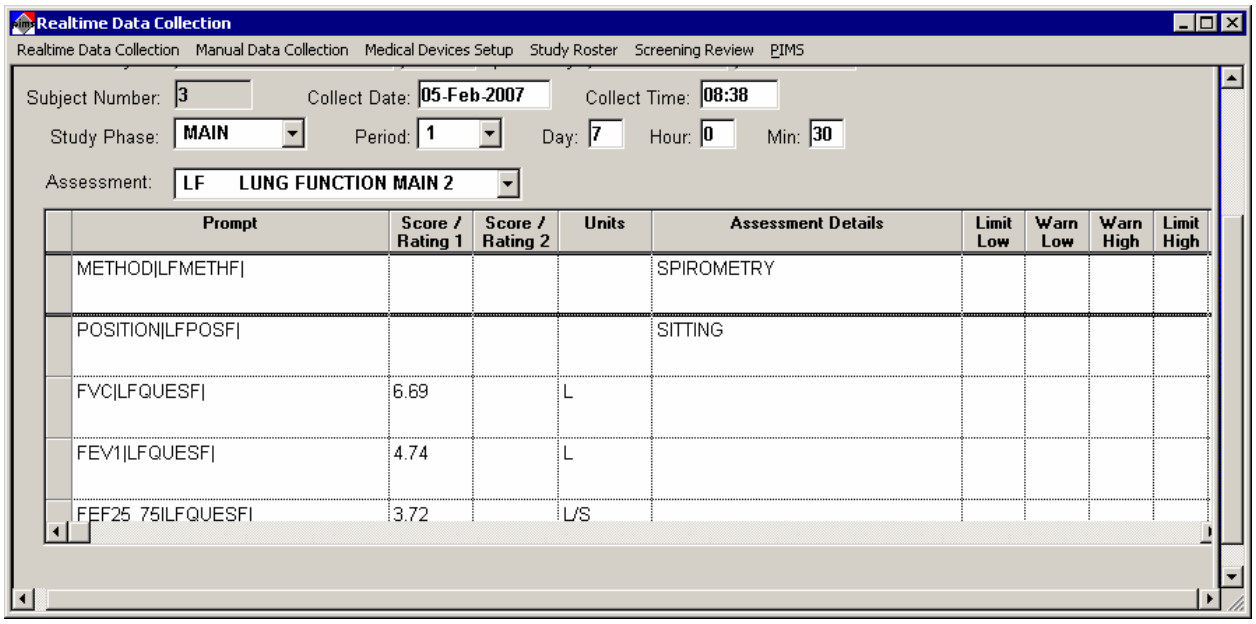
The SGT team continues to work together and to collect metrics on the 24 hour challenge, including lessons learnt after each study, which are communicated and implemented for the next study.

SAFETY AND EFFICACY DATA IN PIMS

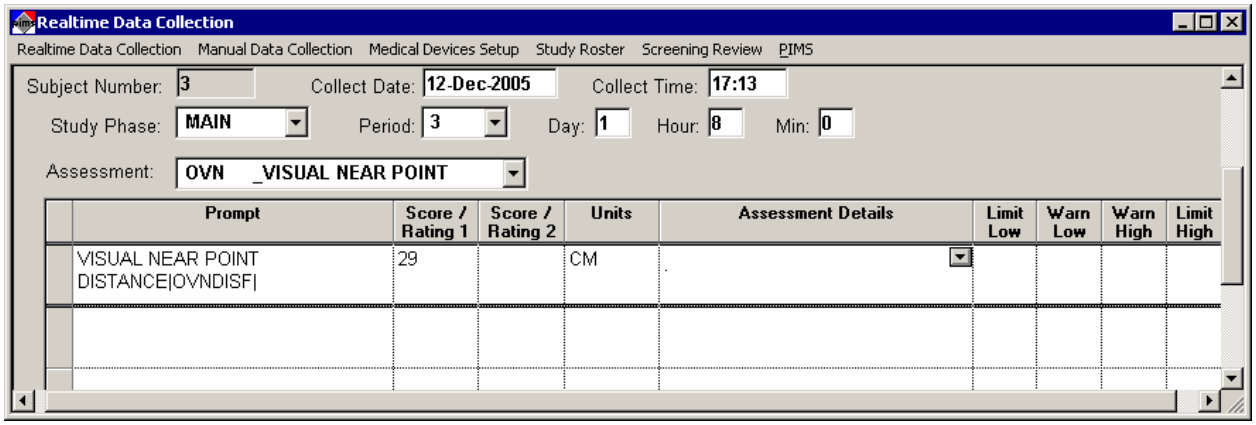
The safety data windows in PIMS were designed to mimic the Pfizer data standards for each data type. However, there is just one window for each safety data type and these are fixed, ie there can be no study level changes to any of these windows. The example demonstrates the vital signs collection window:



This window will be used to collect vital signs data for every PIMS study globally. Similarly, there is only one PIMS window for demography data, concomitant drug and non-drug records, adverse events data, ECG data, medical history, physical examination, subject summary, PK collection and dosing data, etc. There is also only one efficacy assessment window, which again is fixed. However, due to the nature of efficacy data, the window is developed to enable flexibility in the capture of different efficacy data types. The example below depicts the collection of lung function data in the efficacy assessment window:



The same window is use to capture visual near point data:



The first eight characters in the “Assessment” field are used to assign the SAS output dataset name by the extraction code, ie OVN.saseb$data or LF.saseb$data in the above examples.

REPORTING CODE

Pfizer already have a suite of generic safety macros, which are used by the CDARS system to produce standardized safety presentations using the in-house data standards. However, there are several options for each presentation dependant on which data modules are used to database the study data.

For PIMS studies, by ensuring there is only one global generic PIMS safety window per data type, results in just one possible extraction data format for each data type. As a result, the safety reporting macros and their input options are the same across all PIMS studies for each data type, the only changes will be due to study designs. This has significantly facilitated the set up of the standard safety reporting software, enabling all safety presentations to be prepared up front, during study conduct, before database lock.

PROCESSES

Not all Phase 1 studies fall into the “24hour goal”. There are strict criteria which have to be met for clinical study report presentations to be available in 24 hours:

- Studies must run at one of the Pfizer Clinical Research Units.
- Studies must be sponsor open, ie open label studies (where the investigator, subject and sponsor are open) or third party open studies (where the investigator and subject are blinded, but the sponsor is open). For

these studies, the shadow treatment views can be unblinded to the programmers before last subject last visit. This enables the up front production of all the reporting software and presentations using the actual subject treatment records.

- Only presentations of data stored within the PIMS database will be available in the 24 hour period. Some electronically available data types, including pharmacokinetic data (PK), are currently loaded directly onto the OC database. Presentations for these data types are excluded from the "24 hour goal" as these are not part of the PIMS database.

THE REPORTING PROCESS

Once the study is in conduct at a Clinical Research Unit, and subjects have had their initial dose, the statistician can prompt the PCRU pharmacist to break the shadow blind to the programmers. The available data, including un-blind treatment data can then be extracted in CDARS.

For Cohort studies, where there is more than one cohort of subjects, the PCRUs will clean and release the data on a cohort by cohort basis. This enables the data for a whole cohort to be used to set up the data presentations.

To be able to achieve the 24 hour reporting goal, the programmer must ensure all the required data presentations have been produced before the Last Subject Last Visit date. These draft presentations, based on a subset of the real study data, go through a thorough in-house Quality Control process.

At LSLV date, the Clinical research Unit will clean, finalise and lock the PIMS database within 24hours. Once the PIMS database lock notification is received by the programmers, the data for the entire study will be extracted. Presentations will be re-run, and a final, much reduced, QC process is performed. This is all completed within 24 hours of database lock.

By ensuring the data presentations are correct based on the subset of real data during study conduct, significantly reduces the timelines of the post database lock reporting activities.

TEAM BUY-IN

The final hurdle to achieving the "24 hour goal" was team buy-in across all the functional lines to the proposed changes to processes impacting them:

- The Statistician must ensure the Statistical Analysis Plan is final before First Subject First Visit for a study: this ensures the clinical programmers fully understand the reporting requirements for the study and reporting activities can start on the study during study conduct.
- The clinical teams reviews the safety data on an ongoing basis during study conduct using the available data browsers, and highlight any safety concerns early.
- There is no draft tables review process by the study team, ie the study team do not have the opportunity to review the presentations before they are finalized. These are issued once to the study team, after database lock, and they are final. The in-house data standards dictate the appearance of the standard safety presentations. The PIMS data collection windows do not change between studies, consequently the overall appearance of the standard safety presentations will not change between studies. Non-standard presentations, including efficacy, are reviewed by the statistician to ensure the presentations match the specifications outlined in the statistical analysis plan. This occurs when the presentations are produced by the programmer on the subset of data during study conduct.

GOING FORWARD

With the availability of clinical study report presentations in 24 hours for studies conducted at the Clinical Research Unit, a few challenges remain to be addressed:

- The ability to mimic this process for all studies running at the PCRUs, including double blind studies (where the investigator, the subject and the sponsor is blind) and methodology studies.
- With the move within Pfizer to outsourcing the reporting component of the study, ensuring our Functional Service Providers can continue to meet these aggressive timelines, particularly where the planned last subject last visit date can change.
- Could this process be transferred to studies conducted outside the Clinical Research Units, and databased on the oracle clinical database?

CONCLUSION

Is this really 24 hours from last subject last visit? With the use of functional service providers to outsource the clinical programming component of a study, final clinical study presentations have been issued within 24 hours of LSLV. A study conducted at the Singapore clinical research unit had a LSLV date of 12June07. The Clinical Research Unit locked and released the PIMS database at 04:00 on 13June07. The clinical programmers were based in Shanghai. With Singapore and Shanghai in the same time zone, the clinical programmers could start final table production as soon as the database was released, resulting in final clinical study report tables by 09:00 13June – within 24hours of last subject last visit. This is truly a reality!

CONTACT INFORMATION

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

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