IMI1 Final Project Report
Public Summary

Project Acronym: DDMORE

Project Title: Drug Disease Model Resources

Grant Agreement: 115156
Project Duration: 01/03/2011 - 31/08/2016

1. Executive summary

1.1. Project rationale and overall objectives of the project

The process of drug discovery and development requires data and information to be collected from many sources, in particular from complex biological/pathophysiological systems describing disease states and drug actions. Understanding the insights in these data is at the core of successfully bringing new medicines to patients. Modelling and Simulation (M&S) provides a quantitative basis for integrating complex information to enable informed decision making across all stages of drug discovery, development and clinical use. This is the basic concept of Model Informed Drug Discovery and Development (MID3), a vital approach in understanding the benefit/risk profile of a medicine to optimise the outcomes for patients.

M&S analyses are designed to integrate data in a quantitative way, but the potential value of this approach has not been fully achieved for a variety of reasons. In particular a lack of common standards and processes combined with the use of a range of disparate tools, languages and ontologies hampers its full utilization. A heterogeneous environment has made it difficult to share existing knowledge, creating significant gaps in the way experience can be exploited within drug development. The implementation of MID3 can provide a promising solution to these issues.

The Drug Disease Model Resources (DDMoRe) consortium was created to improve the quality, efficiency and cost effectiveness of MID3. The consortium set out to deliver a platform that would provide infrastructure and tools to share models, and knowledge about those models, based on standards to ensure consistency of evidence. The products developed through DDMoRe now can be used by academia, industry and health authorities as a reliable platform to support decision-making about the development and approval of new medicines, and improvement of therapy with existing drugs.

In order to achieve this, the project set out to address common problems experienced across the entire MID3 process:

- Lack of common standards across the different tools used within the remit of MID3
- No single mechanism for defining and working with models using a common "language"
- Difficulty in capturing key information, e.g., assumptions, decisions and outcomes when developing a model
- No publicly available platform for sharing models and knowledge across and between organisations to ensure consistency of evidence or provide a basis for new M&S analyses
- A lack of workflow tools, designed specifically for integrated modelling, which enable automatic traceability and repeatability
- Variable quality in the expertise and knowledge within a modelling team

In order to address these shortcomings, DDMoRe established the following core objectives:

- Enable efficient exchange and integration of modelling activities and outputs across software tools, disciplines and departments within and among organizations.

- Provide standards applicable to all areas of M&S, appropriate for adoption and use by all relevant domain stakeholders.
- Develop an open, publicly available, free-to-use library of models, based on the developed standards, to promote the sharing and re-use of models.
- Develop education concepts and training materials to foster dissemination and adoption of the newly developed DDMoRe products.

1.2. Overall deliverables of the project

DDMoRe has delivered an integrated set of products:

- a set of standards for developing, describing and storing models,
- a model repository to enable access to curated and shared knowledge,
- an interoperability framework, to bridge modelling tools and methodologies to execute a wide range of different modelling approaches,
- a workflow system, to optimise the process of developing models and simulations, and
- a training program to support adoption of the standards, repository and framework.

DDMoRe has established a set of standards that is key to the integration of its products, enabling efficient exchange and reuse of knowledge between stakeholders. This set of standards has been designed both for model and workflow encoding, and for storage and transfer of models and associated metadata. Based on these standards, a set of products has been developed to improve the quality, efficiency and cost effectiveness of MID3.

The **DDMoRe Model Repository**, which is open, publicly available and free-to-use, provides key functionality such as collaborative modelling and sharing of private models, detailed model display, capturing and displaying annotations for models, and importing publications. Only a few months after launch, it already provides access to more than 100 annotated and "ready to use" Pharmacokinetic (PK), Pharmacodynamic (PD), PKPD, physiologically-based PK (PBPK), statistical and systems biology models applied in different therapeutic areas like Oncology, Diabetes and Neuroscience.

The **Interoperability Framework**, through its integrated infrastructure, enables efficient exchange and integration of models across existing and new tools, and modelling languages. It supports model development with the newly developed Model Description Language (MDL), and leverages the system-to-system interchange standards Pharmacometrics Markup Language (PharmML) and its related Standard Output (SO) markup language. In this way it facilitates the execution, via the ddmore R package and the connected target tools, and the re-use of models from the Model Repository. In conjunction this enables users to script seamless workflows integrating a wide range of tools within a M&S approach.

In addition to standards and tools, DDMoRe has delivered a model development **workflow process** standard – named "Thoughtflow" – providing an accessible framework to capture and represent the key steps that form part of the everyday process of model development and evaluation. A project "Thoughtflow" is stored in a dedicated knowledgebase, and is populated both implicitly by monitoring user actions (e.g. adding a file to a version control system, executing a task) and explicitly by the user,

who will document assumptions, take decisions, or perform modelling tasks such as extending or creating a child of a model. The knowledgebase can then be queried to extract the model development "tree" and project information, making it possible to assess the impact of assumptions, and determine the provenance of project decisions.

To drive adoption of its deliverables and products, the **DDMoRe face-to-face course programme** provided a set of training events on the use of DDMoRe products, demonstrating as a proof of concept, how these products can be integrated in modelling and simulation tasks to enable MID3 in 5 key therapeutic areas – Diabetes, Oncology, CNS, Cardiac Safety and Infectious Diseases. Training materials are available online as an extract from the provided face-to-face courses.

1.3. Summary of progress versus plan

The DDMoRe consortium delivered a core set of products at the end of the project that form the cornerstone of its vision, and from which the worldwide scientific community can derive significant benefit. The Model Repository, the Interoperability Framework and the Thoughtflow prototype provide the scientific community with a set of integrated tools designed to address common problems experienced across the entire MID3 process.

The project saw a major growth in momentum at the end of 2014, as the various work package teams moved from working independently to a focus on integrated, concrete products, knowing that these would be the key indicators of success in ensuring that the consortium delivered customer-focused solutions.

Model Repository
The DDMoRe Model Repository is now considered a mature product, with a robust infrastructure already populated with more than 100 diverse free-to-use models. Much of the originally envisaged functionality is in place: submitter registration, team management for collaboration, with the option of sharing private models, detailed model display of models encoded in PharmML (version 0.6.1), scientific publication import, capture and display of model annotations, advanced search, contextual help, automatic publishing process and an option to request a model certification.

From this list, model annotation and certification are the features that will require further development to fully meet the needs identified by end-users. While requirements have been defined for model annotations and a complete certification procedure has been designed, the infrastructure supporting those features is not yet complete. The model annotations captured in the repository are restricted to a limited number of fields; however, behind the scenes, the ontology knowledge base that stores the annotations schema includes more than 80% of the fields identified in the end-user requirements. More work is still needed to display those fields in the user interface, to store corresponding annotations so that modellers can benefit more from the model search functionality, and more efficiently filter to the model of interest.

The certification process is currently handled manually using e-mail exchanges. Ultimately, a system such as the one used by scientific journals to perform article review has been designed and was expected but development of the annotation infrastructure used more resources than anticipated. As of today, the infrastructure for model certification is limited to a webpage describing the process to follow, and an email address used by a dedicated group of reviewers. A design of the required infrastructure has been documented, facilitating further development when resource is available.

Interoperability Framework

A Stand-alone Execution Environment (SEE) version of the Interoperability Framework (IOF) has been made publicly available as a comprehensive software package, enabling efficient exchange and integration of modelling activities and outputs across various M&S software tools and disciplines. The IOF builds on the languages and standards developed within DDMoRe: The Model Description Language (MDL), Pharmacometrics Markup Language (PharmML), Standard Output (SO), and ProbOnto.

The converters, from PharmML to target tool code and from target tool output to SO, enable the IOF to support many commonly used software tools in the M&S field. Defining a new modelling language has been a very ambitious task, and while the key modelling tools are fully supported, some remain partially completed at the project's end. It took more time than expected to harmonise development of MDL and PharmML – a key step to make the model translation between the two languages smoother. As a consequence, this delayed support for some tools. At this point, MDL is closely aligned to PharmML and the set of models and tasks that can be described in MDL and for which translation to PharmML is supported in the MDL-to-PharmML converter is almost equally wide.

The PharmML-to-target-tool converters that have been developed currently support a narrower set of models and tasks. Important gaps include more extensive support for models with count or time-to-event outcomes, with inter-occasion variability, Bayesian models and optimal design. Models with binary or categorical outcomes, with higher levels of variability, with BLQ handling, mixture models, Markov models, advanced residual error models, and input interpolation are also not supported yet.

While the IOF supports execution of models written in MDL, it is also essential to deliver a bi-directional converter, where a model written in a target tool (e.g. NONMEM) could be back-translated into MDL. Development showed that the back-conversion was a more difficult task than anticipated. As the focus of MDL was to support encoding of inter-operable models, this is in some ways more restrictive than a target tool language. The back-conversion needs to handle the different language constraints correctly, and still requires some development resources for a full bi-directional conversion (e.g. from NONMEM to PharmML, Winbugs to PharmML). Converters have been developed for PharmML to MDL, and Monolix to PharmML; the NONMEM to MDL converter requires manual intervention to fully capture the modellers intentions. Nevertheless, a significant number of models are supported, and the objective has been largely achieved.

Workflow

The "Thoughtflow" workflow product, delivered at the end of the project, consists of robust standards for provenance-based workflow capture, storage and retrieval of pharmacometric activities, embedded into a prototype. Pharmacometric workflow components – in terms of activities, entities and agents – are defined and captured based on an extended version of the PROV-O ontology (http://www.w3.org/TR/prov-o/). PROV-O was not identified in the description of work, however it is an evolving World Wide Web Consortium (W3C) standard that captures the provenance and relationships between items, as well as audit trail information (who did what, when, and how) required for a workflow environment.

While it took some time to find the best-suited workflow environment to start from, the use of PROV-O represents clear, innovative thinking for the modelling community.

After it became clear that there were insufficient software development resources available in the project to support the creation of a production-ready software tool as listed in the description of work, a set of prototype demonstrator tools was developed that integrate the new standards. Although not yet suitable for production use, the tools are cross-platform (supporting all commonly-used operating systems) and portable, having been designed to provide a basis for further development, with a view to a future version being able to be deployed as painlessly as possible in a range of likely industry, academic and regulatory scenarios.

1.4. Significant achievements

Before the DDMoRe project started, the modelling and simulation (M&S) process was fragmented by the lack of software tools that could exchange data and models with each other, and that could seamlessly cooperate in the same workflows. This resulted in inefficient reuse of data, models and exchange of methods and methodologies. This lack of interoperability across modelling tools, and a lack of M&S standards in general, resulted in large duplication of effort by many stakeholders across the research and development (R&D) process with limited ability to integrate, share and reuse existing knowledge, and limited opportunities to build on knowledge in innovative ways.

At project completion in August 2016, DDMoRe has delivered a set of integrated products and concepts, making a significant advance in addressing those common problems experienced across the entire MID3 spectrum. The five-and-a-half years of development completed by the consortium provided an opportunity to create new integrated, purpose-designed working tools that could not have been delivered by any institution working on its own.
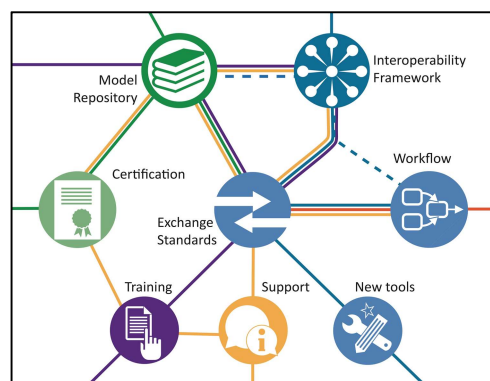
Standards

DDMoRe has created standards for:

i. facilitating communication between analysts about structural and statistical models, independent of any software tool - using the Model Description Language (MDL)

ii. conveying modelling information relevant for translation of these models to target software - using the Pharmacometrics Markup Language (PharmML)

iii. collecting output from target software in a unified and readily accessible form, using the Standard Output (SO) format, and

iv. describing probability distributions and their inter-relationships using the knowledge base ProbOnto.

The project has demonstrated that a wide variety of models can be encoded using these standards - in the Use Cases that we share with the MDL-IDE and also through models encoded in MDL in the DDMoRe Model Repository. The SO format gathers information from analysis output, making it easier to report consistently in the R modelling language; this enables information to be passed seamlessly between modelling and simulation steps, as well as from one tool to another. These tools offer huge potential in facilitating integration of existing and new software, and form the core standards for interoperability and communication of models and modelling outcomes.

Each of the software tools used by modelling professionals has a slightly different way of defining the model. The DDMoRe standards can be used to provide a consistent input and output from these tools, so that they can be integrated quickly into the analyst's toolkit. The Systems Biology Markup Language (SBML) standard has been widely adopted within the systems biology domain as the standard for expressing models and integrating a wide variety of tools. It is our intention that the DDMoRe standards should drive development and innovation of new tools in the same way within the pharmacometrics domain.

Interoperability Framework

The IOF, available to the public as a comprehensive software package, is a unique tool where efficient exchange and integration of modelling activities and outputs across various software tools is possible thanks to the standards that DDMoRe created. During the project we have shown how our DDMoRe standards – MDL, PharmML and the SO – facilitate interoperability across some key modelling and simulation tools (NONMEM, Monolix, WinBUGS, PsN and R packages such as simulx (mlxR), Xpose), and new tools have evolved over the lifetime of the DDMoRe project (e.g. many new R packages such as PKPDsim and mrgsolve supporting modelling and simulation tasks). There is no other package which integrates key modelling tools the community uses every day in one unique user interface, and enables complete execution from start to end of a modelling analysis.

The modelling community has started to understand the value of the IOF during the last two years, as it has been demonstrated at a range of events including a DDMoRe consortium meeting in 2015, the PAGE congress and webinar in June 2016, individual EFPIA company discussions, and the last series of training courses. This has led to very encouraging results, with the different surveys collected after the courses showing good levels of engagement. Modellers can see how, in the near future, the

functionality provided by the IOF could make them more versatile in utilising a range of modelling approaches and save a significant amount of time.

Model Repository

The Model Repository is also now very visible in the modelling community. It has been listed in a survey of how (and if) modellers would like to share their models, conducted by the International Society of Pharmacometrics. Preliminary results of the survey are very encouraging as the DDMoRe repository is listed among the preferred solutions, and show that the repository is visible globally. This is not surprising as the repository is a unique solution offered to the modelling community. It has been specifically designed for modellers, and has the potential to become the repository of reference when any scientist wants to use published models for their own project, as well as when regulatory body assessors from the EMA and FDA need to refer to current knowledge. The repository has significantly changed the way modellers can share their knowledge.

Workflow

The "Thoughtflow" workstream product now provides a fully-realised set of standards for provenance-based pharmacometric workflow capture, storage and retrieval. A white paper submitted for publication in the journal *Clinical Pharmacology & Therapeutics: Pharmacometrics & Systems Pharmacology* (solicited by the journal) describes the novelty of the standards DDMoRe proposes to apply to modelling analyses.

Training

Six face-to-face training events have been delivered during the DDMoRe project across Europe, covering diabetes, oncology, CNS, infectious diseases, and drug safety. In the most recent courses, DDMoRe users were able to successfully perform exercises in a complete workflow simulation, using advanced data and model features (e.g. discrete data, time-to-event) and tasks (e.g. estimation, simulation, optimal design) in 7 different software tools implemented in the IOF. Evaluation of the course by participants after the DDMoRe products training showed high learning benefits on the predefined cognitive complexity levels; 'knowledge', 'skills' and 'attributes'.

DDMoRe Foundation

In May 2016, the DDMoRe Foundation became a legal entity, based in the Netherlands with a Board of 5 members representing academia and industry. The primary objective of the Foundation is to ensure continuity of use for the important public domain deliverables from the DDMoRe Consortium, sustaining the standards and infrastructure while reinvesting income for the benefit of the global community.

To encourage participation, organisations that engage at an early stage will be offered a range of benefits. These will include a private instance of the repository (for Pharmaceutical companies), standards and convertors that support distributed job management, model code checks and user support, customised training, and communication tools that are targeted at a variety of different stakeholder groups.

The Foundation follows a set of design principles:

- **Sustainable**: Able to maintain and grow both standards and infrastructure for the benefit of the global community over time
- **Representative**: Of a broad range of organisation categories within the global community
- **Easily accessible**: Organisations can easily become Foundation Partners and derive benefit from both the public domain and Foundation Partner-specific content and output
- **Financially viable**: Able to generate sufficient revenue to cover costs
- **Not for profit**: Reinvesting income in maintaining/ improving standards and infrastructure for the community
- **Not competitive**: Not a competitor for commercial suppliers, but seeding competition to improve tools for the community
- **Independent**: Autonomous, not relying on financing from, or viewpoint of a particular institution(s)
- **Efficient**: "Lean and mean" organisation, able to make and act on decisions
- **Adaptive:** Able to benefit from a changing environment

1.5. Scientific and technical results/foregrounds of the project

The underlying core of DDMoRe's achievements is a set of standards that enable integration across tools, including:

- The Model Description Language (MDL), which is a unified language for end users/modellers to write their models in – regardless of the software tool they intend to use for a given task – and an associated MDL-to-PharmML converter;
- Pharmacometrics Markup Language (PharmML), which is an XML-based standard for exchange of model, data/design, and task information between software tools;
- Standard Output (SO), which is an XML-based standard for storage and exchange of output from estimation, simulation and optimal design tasks; and
- ProbOnto, which is a knowledge base covering more than 100 different probability distributions, which is used/referenced within PharmML.

DDMoRe's standards have been incorporated into three products: the IOF, the Model Repository and the Thoughtflow workflow process. The products have been presented, demonstrated, initially deployed to some partners and most importantly used in multiple training courses.
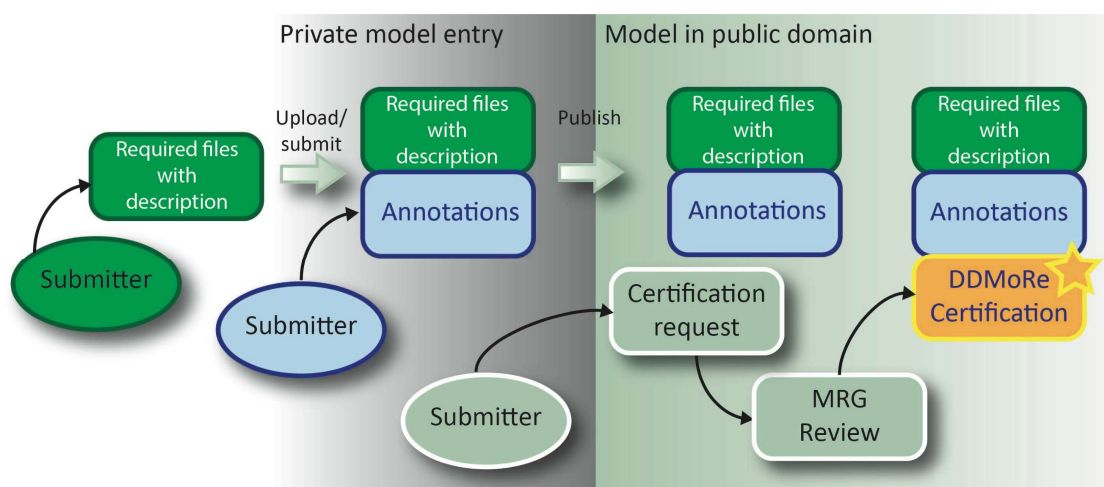
Model Repository

Launched publicly in August 2016, the DDMoRe Model Repository is a web-based interface offering free public access to a curated collection of annotated and "ready to be used" drug and disease models. Now populated with more than 100 models, the content consists of Pharmacokinetic (PK), Pharmacodynamic (PD), PKPD, physiologically-based PK (PBPK), statistical and systems biology models applied in different therapeutic areas like Oncology, Diabetes and Neuroscience.

At launch populated with 80 models, the repository has meanwhile gained an additional 20 models. Half of the models in the Repository are currently interoperable via the PharmML and MDL exchange

standards wile the remainder consist of target code submissions. The web site offers full functionalities to the public and partners in DDMoRe IMI consortium, including:

- submitter registration,
- team management to collaborate and share private models,
- detailed model display for models encoded in PharmML,
- publication import,
- model annotations capture and display,
- advanced search,
- contextual help,
- and an automatic publishing process.

For a published model entry, a submitter can request a review to obtain a DDMoRe model certification. Performed by the Model Review Group (a group of expert modellers with experience in the DDMoRe framework), the review will ensure that a model displayed as certified is completely documented, can be executed using the DDMoRe IOF tools and reproduces key findings reported in the associated publication. The review process is documented in the Model Qualification Procedure (MQP) published online on the DDMoRe website.

Tutorials have been created to help users to take full advantage of the repository. All necessary documentation has been compiled to allow any institution to install the repository privately and fill it with its own drug and disease models and their related content (including proprietary data) in a secure way. Finally, identified issues have been listed and a proposal for additional development tasks has been transferred to the DDMoRe Foundation board in order to optimize the next phases of development.

Interoperability Framework

DDMoRe has made a comprehensive software package publicly available that enables efficient exchange and integration of modelling activities and outputs across various software tools and disciplines within the M&S field.

The IOF builds on the languages and standards developed within DDMoRe. Many commonly used software tools in the M&S field are supported by the IOF, because converters from PharmML to target tool code and from target tool output to SO have been developed:

- NONMEM, Monolix, and WinBUGS for estimation,

- PsN for bootstrap and VPC,

- PFIM and PopED for optimal design (partially supported), and

- Simulx and SimCyp (both partially supported) for simulation.

The software provides support for seamless execution of a full modelling analysis from graphical exploration to model simulation, where the model is coded only once but used in many target tools. End-users/modellers interact with the IOF via the MDL Integrated Development Environment (MDL-IDE), which is a graphical user interface featuring an MDL editor for writing models in MDL and an R console for executing R scripts. Using R as the scripting language for controlling analysis workflows within the IOF has the advantage that R is already widely used by the Modelling and Simulation community, that all functionalities of R (including the many freely available R packages) are available to the user, and users can write and use their own functions or R packages. In practice, within the IOF users control execution of tasks in the supported software tools from R by means of the functions and utilities made available in the ddmore R package.

The different target software tools have varying capacities and underlying assumptions, and it is therefore a prerequisite for achieving interoperability that the user plans ahead and encodes the model in MDL in a way that is designed to be interoperable. This means that using the IOF will minimise the duplication of effort often seen in the M&S process by facilitating re-use of models or parts of models across software tools; it will also improve quality and ensure reproducibility of M&S analyses, because analysis workflows can be scripted end-to-end within R scripts.

Technically, the integration of software tools within the IOF is facilitated by the Framework Integration Service (FIS) and the Task Execution Service (TES), as well as by a connector API through which connectors to third-party software tools can be created.

The XML-based standards (PharmML, SO, probOnto) are mature and well-tested, and a very wide set of models and tasks are supported by these standards. The MDL is closely aligned to PharmML and the set of models and tasks that can be described in MDL and for which translation to PharmML is supported in the MDL-to-PharmML converter is almost equally wide.

By the end of the DDMoRe project, the languages, standards and software components delivered as part of the IOF are generally at a mature stage, but gaps remain, providing an initial focus for the newly formed DDMoRe Foundation. It is possible for users to automatically convert existing NONMEM or Monolix models into MDL, but it is currently not easy, because the available conversion tools (nt2mdl for NMTRAN-to-MDL conversion, and MLXTRAN-to-PharmML and PharmML-to-MDL) are stand-alone tools that have not yet been integrated with the IOF (neither directly in the MDL-IDE nor via the ddmore R package).

***Stand-alone Execution Environment (SEE) of the IOF***

The SEE version of the IOF is meant to serve as a demonstrator, showing that interoperability between software tools and across disciplines can be achieved via the DDMoRe standards. In practice, within many organisations, the components of the IOF will need to be integrated within the existing IT infrastructure, which is achievable as the components have been designed in a modular fashion, where each component can be used as a stand-alone tool.

Through a series of pilots within EPFIA companies, we have demonstrated that integration within existing IT infrastructure is feasible across different server operating systems (Linux, Windows), different scheduling/grid engines (LSF, SGE, OGS), and with different software tools (NONMEM, PsN, Monolix).

The delivery of evolving public instances of the IOF also showed that many individual users could install the IOF quite simply themselves locally on their own computers. Through different installation cycles and the number of modellers involved, many of the bugs and ambiguities in the installation documentation have been solved. The local version includes a temporary license for NONMEM and Monolix, and facilitates quick execution of modelling tests. In this context, because of the complexity to set up a temporary embedded target tool license in the IOF and because of other priorities such as the bi-directional converters, the web instance of the IOF has not been further considered during the project.

IOF Use Case

With the IOF, the end user/modeller experiences a non-fragmented M&S process, where he/she only has to encode the model once (in MDL) and can then use the functions/utilities available in the ddmore R package as well as the target software tools supported by the IOF to define an end-to-end analysis workflow within a single R script.
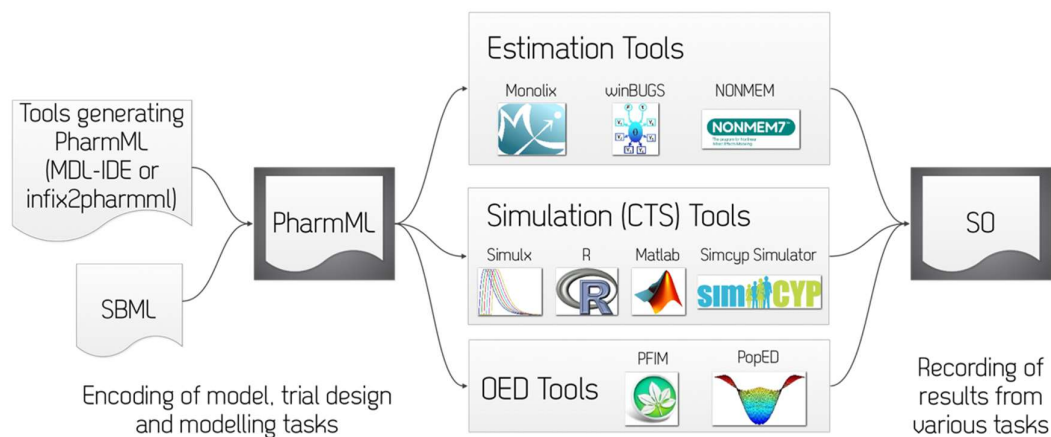
An example of this kind of analysis workflow could be data exploration in R, followed by model development/estimation in NONMEM, model diagnostics in Xpose (an R package), bootstrap and VPC in PsN, trial design optimisation in PFIM, and trial simulation in Simulx. The end user/modeller can easily share their model (and R script) with colleagues who use different tools, and they will still be able to run the analysis, only with e.g. Monolix instead of NONMEM and/or PopED instead of PFIM. It is even possible to share the model with colleagues who use Bayesian analysis approaches, and they will only have to define a suitable prior before using the model for analyses in WinBUGS. SimCyp

users can use SimCyp to define analysis populations or obtain simulation data, which can then be imported into the IOF and used for further analysis within the framework.

Thoughtflow – a Pharmacometrics Standard Workflow

DDMoRe has delivered a more advanced set of standards that complements the ddmore R package embedded in the IOF. Named "Thoughtflow", this set of standards gives users a means to track, record, and report pharmacometric activities across all phases of drug discovery and development, either in part or as an entire analysis. It is centered on the concept of provenance, which defines the relationships between entities and activities in a more useful and comprehensive way than traditional workflow tools. The definition and capture of pharmacometric workflow components, in terms of activities, entities and agents, is based on an extended version of the PROV-O ontology, a World Wide Web Consortium standard that captures the provenance and relationships between items, as well as audit trail information (who did what, when, and how) required for a workflow environment.

Accompanying the standards, a set of prototype demonstrator tools has been developed. It is comprised of several linked components:

- **Provenance database**: a "triplestore" – a database designed for the storage and retrieval of linked provenance information
- **Provenance infrastructure:** monitors user actions and automates actions such as adding files to the provenance database
- **Provenance services**: provides queries to add, update and retrieve information from the provenance database
- **Version control system**: used to unambiguously and reproducibly identify all entities within a project
- A **graphical user interface (GUI)**, and
- Satellite tools enabling reporting and visualization based on queries of the database.

Although not yet suitable for production use, the tools are cross-platform (supporting all commonly-used operating systems) and portable, having been designed to provide a basis for further development, with a view to being able to deploy a future version as painlessly as possible in a range of likely industry, academic and regulatory scenarios. All prototype demonstrator components are available for download and work for a limited range of test cases.
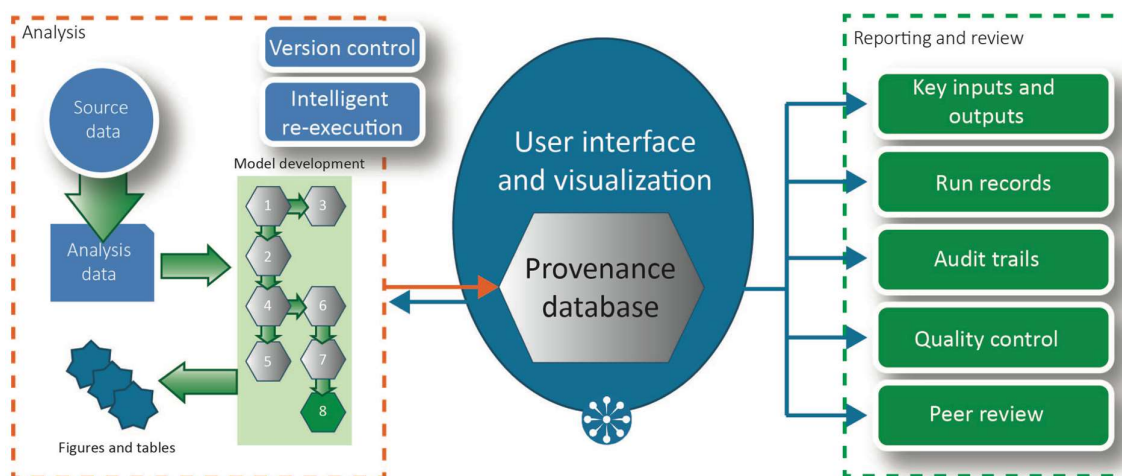
Inputs, scripts, models, outputs and decisions are versioned and their provenance is tracked

A lightweight but powerful GUI brings visualization and control

The database can be queried to streamline reporting and review

1.6. Potential impact and main dissemination activities and exploitation of results

Impact

DDMoRe as a whole

Two of the key issues that industry faces in providing new medicines for society are how to reduce the escalating costs of drug development, and how to make informed choices about where to invest to get the best return for all stakeholders. MID3 has been conceived as an approach to solving these issues, when consistently utilised. The value of modelling and simulation in reducing the cost of developing new drugs and improving the speed of the process can only be achieved by providing reproducible, transparent models to serve as a strong evidence base for regulatory submissions to apply for marketing approval. The DDMoRe framework has been developed to meet this important need for MID3 stakeholders.

While many new models are published every year, few articles detail a model sufficiently well to enable other researchers to reproduce the results. To date, the DDMoRe free-to-use set of products and standards are the only one in the public domain to provide all of the core functionality required to deliver high quality, reproducible models. DDMoRe is evidence of Europe clearly taking a leading role in this respect, providing the worldwide scientific community with new opportunities in quantitative knowledge integration.

DDMoRe's Thoughtflow product offers industry an outlook towards an integrated tool to capture workflow information – a good way to retain and transfer knowledge supporting model continuity for transition and translation phases, and essential for ensuring quality. Such an approach can also support

stronger regulatory submissions by recording metadata and other source (input) information, modelling and simulation outputs, assumptions, extrapolation, interpretation, decisions and documentation.

Providing the consistent, integrated infrastructure to enable regulatory agencies to engage most effectively with M&S is a key value proposition for DDMoRe. As the main 'public facing' tool from DDMoRe, the Model Repository provides a free repository offering a reference resource for regulators to challenge and influence modelling analyses that they review and advise on. In so doing, there is an expectation that analyses used in a regulatory submission will be of higher quality, and transparently facilitate alignment between sponsors and regulators, improving the speed of review and thus access to medicines for patients. It will also provide a continuous learning loop to further improve the use of models as a vital tool in evidence-based medicine.

The model certification process is an important part of the value proposition, increasing the transparency and resulting trust in models. Knowing that the information submitted has been scrutinized by an independent group of modelling experts increases the degree of trust that external stakeholders can have in the results, with a further assurance that the model code is executable and replicates the published one, providing confidence in its reproducibility.

The potential for the DDMoRe framework to improve the flow of new medicines is also based on providing a streamlined, efficient approach for modellers to create and re-use models. In the same way as standard communication protocols were required to realise the value of Internet technologies, DDMoRe's IOF and Thoughtflow provide a strong set of standards and tools to help modellers using different approaches to translate quickly and accurately between them. This preserves the flexibility of using the right tool for a particular task, whilst removing the wasted time and money spent trying to understand, re-code and run published models (which are often the starting point for an analysis).

When the IOF became mature enough to show-case a complete analysis from start to end, a one-day workshop (supported by a one-hour webinar), was presented to more than 100 modellers. This showed how modellers could interact with the framework, and introduced the graphical user interface that enables modellers to easily write models in MDL and execute R scripts. Modellers saw that MDL was easy to read and understand, and that execution of modelling analysis was seamless as it was done only using one R-based script. People attending the demonstrations of working tools commented that they could see how they could save time in their daily hands-on tasks, reducing the number of manual errors that are otherwise very hard to avoid when many steps are required to complete an analysis.

The Thoughtflow standards and prototype were created to meet a crucial need in the MID3 domain – the ability to easily capture, track and report all aspects of a pharmacometrics analysis in a standardised and comprehensive manner, essential to follow Good Clinical Practice principles and adhere to compliance with regulatory guidelines and requirements.

Appropriate use of the standards and tools to automate aspects of pharmacometric model development will save time, reduce transcriptional errors, enhance transparency, support the retention and transfer of knowledge, encourage good practice and help ensure that pharmacometric

analyses impact decisions appropriately. The ability to document, communicate and reconstruct a complete pharmacometric analysis using an open standard has considerable benefits for pharmaceutical research and development; we believe that the associated increases in efficiency and development speed and quality will bring the appropriate drugs to patients faster.

The use of existing, well-established standards means that a set of tools for visualising relationships in data is already available, and tools developed by DDMoRe and its successors are likely to be easily supportable. The use of ubiquitous open standards and software to establish a Thoughtflow is a strong cornerstone for future development, since the pool of developers familiar with these technologies is large. The public standard is being implemented in commercial and open source software tools, which increases the likelihood of additional organisations engaging in further development. A continued set of publicity activities, including conference presentations and papers in appropriate journals, is being conducted to ensure that DDMoRe's products remain firmly in the minds of modellers, globally.

A future benefit of the DDMoRe M&S environment could be to improve the use of models used every day in hospitals to monitor drug concentrations and efficacy or safety signals, for instance in intensive care units or units dealing with infectious diseases. DDMoRe's model repository such the one DDMoRe developed could definitely help hospitals to point to the same model of reference and improve in a collaborative manner the way treatment adjustments in patients happen.

With DDMoRe's products positioned to deliver real value for medical research, IMI investment in this initiative has enabled Europe to provide leadership and derive early benefit from this type of collaborative thinking and provides a new way of achieving major improvements in industrial processes that have an important societal impact. There is a growing environment of partnership in pharmaceutical R&D, seen in the work of organisations like IMI and C-Path, which rely for their success on improved knowledge management. The enhanced knowledge sharing achieved during the project, and facilitated in the future by DDMoRe's products, will improve the process of getting new medicines to patients, supporting the triple helix of industry, academia and health authorities.

Communication

The DDMoRe project had a specific work stream on communications to ensure that the value of the framework being developed was broadly communicated. A coordinated set of activities has been conducted to disseminate knowledge about the framework and the individual products:
- a comprehensive face-to-face training and education programme
- webinars, workshops, symposia and stands at different scientific congresses (in US, Europe and global conferences),
- initiation of a partnership with a key scientific journal of the community,
- several meetings with regulatory assessors from EMA and FDA.

Training & Education

Core to DDMoRe's communication plan has been a dedicated training and education program. This has increased visibility of the different tools developed by DDMoRe, and also demonstrated, using

adapted examples, the added value of the integrated solution DDMoRe has delivered for the community.

Training events had over 100 attendees, with course participants indicating that they received very valuable learning benefits in developing knowledge and skills on DDMoRe's products.

All of the face-to-face courses gave substantial feedback about the end-user's opinions with respect to the developed DDMoRe products, the DDMoRe training and the DDMoRe initiative, including the sustainability aspects of the project e.g. features, functionalities, usefulness, applicability, benefits, implementation in daily work/working infrastructure, further ideas/developments, and training needs.

During the final face-to-face training course (the first advanced course), new DDMoRe users were able to successfully perform exercises in a complete workflow using advanced data and model features (e.g. discrete data, time-to-event) and tasks (e.g. estimation, simulation, optimal design) in 7 different software tools implemented in the IOF of DDMoRe.

Course materials for web-based training have been extracted from five DDMoRe face-to-face test-run training events, to cover training on:
- the DDMoRe products (standards: MDL, PharmML, Standard Output, ddmore R package; platform/software: MDL-IDE, model repository and certification, Interoperability Framework, workflow concept)
- Model-informed Drug Development in five Therapeutic Areas (TA), giving (i) an introduction in the TA oncology, diabetes, CNS diseases, infectious diseases and cardiac safety, and (ii) exercises covering a broad spectrum of highly relevant preclinical, translational and clinical models in the TA and tasks/workflows (exploratory analyses, estimation, evaluation, simulation, optimal design) as well as providing the solution to the exercises.

For the web-based self-educational training, animated tools have been developed to help increase competence levels of scientists new to the field http://www.ddmore.eu/product/training

The curriculum framework and all course materials, as well as the evaluation and feedback forms, were continuously developed and delivered at the time of the following courses:
- DDMoRe F2F training course in "Model-informed Drug Development (MIDD) in Oncology (Beginners)", Berlin/Germany (March 2015)
- DDMoRe F2F training course in "MIDD in CNS diseases", Leiden/The Netherlands (July 2015),
- DDMoRe F2F training course in "MIDD in Cardiac Safety", Mölndal/Sweden (January 2016),
- DDMoRe F2F training course in "MIDD in Infectious Diseases", Uppsala/Sweden (February 2016),
- DDMoRe F2F training course in "MIDD in Oncology (Advanced)", Pavia/Italy (July 2016).

Stakeholder Engagement

Initial communications activities focused on press releases and newsletters, which have continued to be produced regularly throughout the life of the project. These have been published on the project website, which was regularly maintained, and were sent to a broad set of contacts with an interest in modelling and simulation. Several of the consortium members actively promoted DDMoRe activities through regular posts on LinkedIn and Twitter.

As the intended product offering became clear in early 2014, with the products becoming more robust and mature, a communications plan was triggered, with DDMoRe conducting a significant number of dissemination activities. Most importantly, this has included 5 International congresses – in particular

attendance at PAGE three times in Europe and twice at ACOP in the US – where there have been well-received oral presentations and poster sessions on DDMoRe. While it is acknowledged that this activity should continue and expand outside Europe under the leadership of the Foundation, the level of communication so far ensured an acceptable visibility across Europe. DDMoRe has been cited in other more disease specific conferences, and some journals have invited DDMoRe to contribute papers.

Installation of the platform in EFPIA companies complemented the classroom training, demonstrating that it was possible to integrate the framework in a regulated IT environment. DDMoRe conducted a 'roadshow', briefing pharmaceutical companies on the theory behind the tools and their practical implementation. The prototype Interoperability Framework has so far been implemented in 3 different EFPIA companies, with plans for several more deployments within the next 12 months as responsibility transitions to the DDMoRe Foundation. While the limitation of the currently available converters means that modellers can't entirely switch to the DDMoRe platform to analyse all of their current projects, the recent survey has shown that modellers understand the value proposition. Ensuring that this interest converts into future active contributions is a key activity for the Foundation.

In preparing a communication strategy, DDMoRe identified regulatory agencies and scientific journals as key stakeholders in the success of the framework that were not part of the consortium. Regulatory agencies in Europe and the US were identified as the highest priority, and DDMoRe has had regular interactions with representatives of EMA and FDA to seek guidance and communicate progress. The consortium also approached CPT:PSP, the leading pharmacometrics journal, which agreed to support DDMoRe in publicising its work and the contents of the model repository as it will become populated.

After the first two-and-half years of the project, the consortium conducted an anonymous survey with all the pharmaceutical company members to measure satisfaction with the ongoing progress for each of the individual work packages, and to understand current expectations for DDMoRe's project outcomes. Across the different work streams, respondents were generally satisfied with the completed tasks at that point, although the level of engagement from academia was generally viewed as higher than industry. The survey also highlighted the importance of fostering communications and sustaining engagement between all partners to deliver the project successfully. As a result of the survey, an EFPIA working group was put in place to ensure that end-user requirements and expectations were continually monitored; this work continued for the remainder of the project, and lead to a more regular and intense engagement from EFPIA partners, ultimately sharing the effort equally to bring the Foundation to life.

1.7. Lessons learned and further opportunities for research

The collaboration between the many partners on the project has been extremely positive. Even though personnel were distributed both geographically and across very different domains of expertise, this generated profound discussions, and provided new and exciting ideas. A desire to reach common goals was clear.

DDMoRe demonstrates the importance of standards and quality in Drug Discovery and Development, showing that interoperability between M&S software tools is possible, and that structured knowledge

sharing – both within industry and between industry and academia – can deliver major value. The changes in society's healthcare needs during the course of the project reinforce the continuing importance of DDMoRe project's objectives and the scientific ideas underpinning it; finding better ways to discover, develop and bring new medicines to patients is more relevant than ever.

It is clear that the move from theory and research to working on the development of actual products was a pivotal moment for the project, e.g. the release of the first version of PharmML, providing tangible evidence of progress. On such a long project, identifying milestones that galvanise and inspire the team is very important; it is also important to ensure that their completion is well communicated and celebrated. Equally important is the need to communicate success when a team overcomes particular challenges.

There are undoubtedly areas where performance could have been improved; a key one was project management and coordination, since DDMoRe involved more than 26 partners. Different aspects have been identified:

- Plan: the Description of Work is a long document, but written at a very high level. This meant that a number of requirements of the project were not immediately obvious until details were analysed. This resulted in a lot of 'hidden' work and a lack of clarity regarding expectations and which elements of the plan DDMoRe might not be able to deliver. The project initially seemed very ambitious, without enough focus on the real customer need. Uncertainty about the development outcomes of the products and future engagement of partners appeared; hence after three years into the project, an additional management layer was added. Integration groups were created with committed team members that were to achieve the planned deliverables in the allotted time with a main focus on the delivery of DDMoRe products focused on customer needs.
- People: throughout the duration of the project, there were difficulties around ensuring that the right people from the right partners were available at the right time to produce useful deliverables. There was an imbalance in commitment between institutions, with some people joining and rapidly leaving again, with an inevitable impact as the learning curve for new members of the project was steep. The most engaged people had an ever increasing demand of their time. The required inputs were also not always easy to obtain – for example, in the early stage of the development, end-user insights could not provide relevant input to the MDL-IDE development.
- Progress: Overall, progress in developing the products has been judged as rather slow. This can often be the case with products 'designed by committee', showing a slower development rate than a commercial undertaking. It was rather challenging to find common areas of interest between academic and industry partners concerning the required features of the products to be delivered, with point of views often conflicting. Influenced by these frustrations, work on the deliverables was sometimes driven by short-term commitments rather than an overall strategic plan, limiting productivity at the end.
- SME involvement in consortia delivering open source assets: An important observation from the consortium's experience is that SME involvement as full consortium partners in projects of the scale of IMI is not always appropriate, with clear challenges in generating revenues that make involvement sustainable. The amount of investment required during the life of this kind

of project is large, and as the intention of DDMoRe was to make the results open source at the end of the project, the opportunities for recouping investments were small. Building another product layer on top of the IP generated that could subsequently be sold may be a solution. But this would be challenge as it required an organisation to maintain investment in two groups of developers – one serving an IMI project with open source deliverables itself, and another to build on top of the IP – both of which would need to be funded. Of course, any "product" developed in this way would compete with the open-source IMI deliverables but if that would generate better products it would justify the public investment made.

While DDMoRe objectives are still relevant by the end of the project, further opportunities for research emerged in the last 6 months of the DDMoRe project when the scientific community started to see live-demonstrations of the DDMoRe products. Model interoperability was shown with 7 different target tools, and the Model Repository by that time was filled with 80 models.

Modellers expressed positive feedback regarding those deliverables. To support the concept of MID3 defined earlier in the report, the Pharmaceutical industry would benefit greatly funding further development of the standards DDMoRe created and of the DDMoRe model repository. Maintaining global modelling standards remains a long-term perspective, and before they can be used throughout entire modelling projects they have to be developed further to cover all relevant modelling features used in Pharmacometrics. The DDMoRe Model Repository is already a workable solution to avoid starting from scratch for new modelling projects, but it would benefit from a more user friendly interface to facilitate the user experience, with respect to model curation, or enhanced model annotation.

The Interoperability Framework (IOF) has been delivered to a high level of maturity useful to many modellers at this stage. But improvements in functionality, an enhanced integration with the Repository, and likely more modularity to use it in a production environment, e.g. an Industry or Regulatory setting, would be required to make the IOF a success with all stakeholders.

Those are the main reasons why the strategy of the Foundation will focus on enhancing the Repository, improving the IOF and ensuring continued development of the standards. Further opportunities have been generated recently by releasing the prototype for a "Workflow/Thoughtflow" environment; this new concept has a lot of potential, which can materialize into a full product if enough new partners join the Foundation.