Invitation to become a DDMoRe Foundation Partner:

2016/17 Intake

On behalf of the DDMoRe Foundation Board:

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Introduction

This document serves as an invitation to become a partner of the Drug Disease Modelling Resources (DDMoRe) Foundation.

The DDMoRe Foundation has the objective “to deliver and improve infrastructure to contribute to the quality, efficiency and cost effectiveness of Model-Informed Drug Discovery & Development (MID3) and Therapeutic Use.”

The DDMoRe Foundation has been established to maintain and enhance content delivered by the DDMoRe Consortium, and follows a set of distinct design principles which define its structure, governance and deliverables. A minimum of four financially contributing partners, so called “early adopters”, are required to enable the DDMoRe Foundation to successfully complete a “start-up” phase (the specifics, objectives and timeline of which are detailed in this document).

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The DDMoRe Foundation *Purpose*:

- **Maintain and enhance public domain content from the DDMoRe Consortium**
- **Provide specific DDMoRe Foundation Partner benefits**
- **Increase DDMoRe utilization and global awareness**
- **Expand DDMoRe functionally according to the wishes of the DDMoRe Foundation Partners**

A *Drug Disease Model Resources (DDMoRe) Foundation* has been established to maintain and enhance the content delivered into the public domain by the European Unions' *Innovative Medicines Initiative, DDMoRe Consortium.*

The objective of the DDMoRe Consortium was to improve the quality, efficiency and cost effectiveness of *Model-Informed Drug Discovery & Development (MID3).* MID3 has been defined as a ''quantitative framework for prediction and extrapolation, centred on knowledge and inference generated from integrated models of compound, mechanism and disease level data and aimed at improving the quality, efficiency and cost effectiveness of decision making''[1].

The DDMoRe Consortium (ended August 2016) has delivered a range of exchange standards, systems and tools into the public domain that enable the sharing of models and expertise within and between companies, regulatory authorities, academic institutions and the burgeoning "quantitative community" at large. The DDMoRe infrastructure components provide a platform for MID3 related collaborations across drug discovery and development, with the interoperability framework using DDMoRe standards enabling the efficient exchange of models originating from a variety of independent modelling languages. Adoption and utilization of the DDMoRe infrastructure can reduce the complexity, cost, time and inefficiency of drug discovery and development through effective re-use (feedback and feed forward) of "qualified" models and greatly increases the transparency and reproducibility of modelling outputs and their associated inference.

The DDMoRe Foundation will also provide a variety of *Foundation Partner* specific benefits (in addition to sustaining and fostering the DDMoRe Consortium legacy) and be a catalyst for further developments and enhancements in this quantitative arena that service the needs of a broader *Global Foundation Partnership* as a whole. The foundation is also open towards any interested party; including organizations which were, or were not, part of the IMI DDMoRe consortium during its lifetime.

[1] EFPIA MID3 Workgroup, Marshall et al. CPT Pharmacometrics System Pharmacology 2016

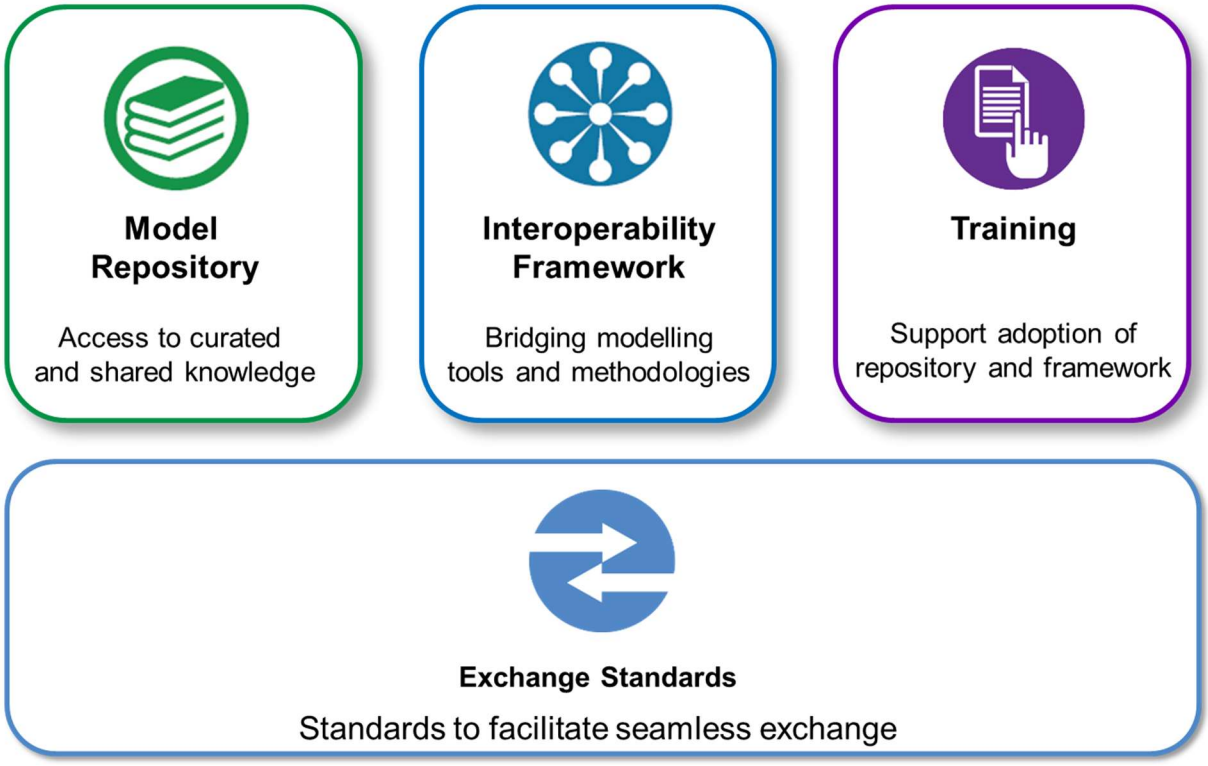
The DDMoRe Foundation "*Early Adopters*":

Are required to:

- **Ensure the public domain DDMoRe content continuity**
- **Enable the "start-up" phase of the DDMoRe Foundation following transition of exchange standards, systems and tools from the DDMoRe Consortium**
- **Assist the Foundation Board in setting the strategic direction and priorities for the Foundation during the start-up phase and beyond**

The "start-up" phase of the DDMoRe Foundation will principally concern four components (Figure 1) inherited from the DDMoRe Consortium and delivered into the public domain.

Figure 1. Focus of "start-up" phase of the DDMoRe Foundation



The DDMoRe Foundation will:

1) *Maintain the exchange standards, Pharmacometrics Markup Language (PharmML), and Model Description Language (MDL):* PharmML is an XML based format, for encoding of models, associated tasks and their annotations[2]. It represents a standard across different tools and can be translated into related tool specific languages. MDL is a human writeable and human readable language that describes pharmacometric models. It is designed to be compatible with (and independent of) a wide range of target tools. MDL facilitates clear and unambiguous definition of models, with information conveyed in a consistent manner to the PharmML representation and onwards towards target software specific code. These exchange standards enable efficient implementation of modelling processes.
2) *Maintain the DDMoRe Model Repository:* The repository is an open, publicly available, and free-to-use resource of models (some of which possess particular DDMoRe certified model code attributes). The Repository is indexed, searchable, and stored models can be supported by a peer review process. Adoption of DDMoRe exchange standards will enable display and search of key model features and elements via a structured and curated annotation system. The model repository has currently over 80 drug- and disease models consisting of published pharmacokinetic (PK), pharmacodynamic (PD), PKPD, physiologically-based PK (PBPK), statistical and systems biology models, of which over 40 are currently interoperable via the PharmML and MDL exchange standards. Adoption of the exchange standards facilitates re-use and sharing of models from the Model Repository, enabling community collaborations.
3) *Maintain and improve the DDMoRe Interoperability Framework:* The framework is an infrastructure that enables efficient exchange and integration of models, and the associated outputs, across modelling languages for existing and new tools. Within the Interoperability Framework *Converters* from PharmML to the currently supported target tools (NONMEM, MONOLIX, PsN, PFIM, PopED and WinBugs) are embedded, all of which are publically available. The Interoperability Framework utilizes the exchange standards, MDL and PharmML, and additionally the Standard Output (SO). SO is another tool-independent exchange XML-based format, intended for storage of results in a standardised form. It enables effective data exchange within complex workflows as well as supports users in assessing, reviewing and reporting modelling steps.
4) *Provide a range of training materials on the exchange standards, the repository and the whole set of DDMoRe developed tools:* These will continue to be made available for the community at large.

In addition, as DDMoRe Foundation "early adopters" Foundation Partners will have immediate access to a variety of Partner specific benefits. These benefits include:

1) *A private version of the DDMoRe Repository:* As described earlier, the public domain DDMoRe Repository enables the sharing of drug and disease models and their related content (including pre-competitive data). A private version of the DDMoRe Repository can be provided, which enables the sharing of *proprietary* drug and disease models and their related content (including proprietary data) within an organization. These two versions of the

[2] Pharmacometrics Markup Language (PharmML): Opening New Perspectives for Model Exchange in Drug Development, Swat et al. CPT Pharmacometrics System Pharmacology 2015

repositories work in tandem, with appropriate security privileges, to preserve the level of access to an organizations' specific content and artefacts.

2) *An alternative version of interoperability framework:* DDMoRe Foundation Partners can receive support to implement a version of the interoperability framework that is compatible with distributed environments and infrastructure in order to promote DDMoRe product integration, content sharing and effective collaborations within an organization. We are anticipating this development but it is contingent on sufficient partners joining.
3) *Early development releases:* Any development facilitated, supported and funded by the DDMoRe Foundation will be made available to DDMoRe Foundation Partners at the time of its completion which might be earlier than the completion of a subsequent public release.
4) *Customized training and support:* DDMoRe Foundation Partners can receive basic training sessions (which can be provided as in-house "hands-on" offerings) that build on the public domain training materials, customized to the needs of that organization. In addition the DDMoRe Foundation will provide its Partners access to subject matter experts who can provide guidance and coaching on DDMoRe exchange standards, repository and tools.
5) *DDMoRe Foundation Accreditation:* An accreditation scheme is envisioned for those DDMoRe Foundation Partners that provide services, e.g., academic groups offering advanced training for DDMoRe Foundation Partners (at a reduced fee) or basic/advanced training for the broader community. The intention of the accreditation scheme is to give the commissioner of work reassurance that the provider can deliver the particular service to a specific DDMoRe standard.
6) *Academic Partner specific benefits:* The potential exists for DDMoRe supported/sponsored research to be pursued and for the DDMoRe Foundation itself, to seek support for external funding bodies. For academic groups that develop methodologies and/or tools, the potential exists for the broader Global Foundation Partnership to assist their endeavours through testing and implementation of their methodologies and/or tools.
7) *Exert their influence on the DDMoRe Foundation strategies, short, medium and long term:* The DDMoRe Foundation Board provides in Appendix 1 a detailed set of proposed components that should be a) maintained in the public domain and b) be provided as DDMoRe Foundation Partner specific benefits. The content of these tables will be discussed in greater detail subsequently in this document. An "early adopter" Foundation Partner will have the unique opportunity to influence both the choices made for the "start-up" phase and the subsequent phase 2 and 3 developments and enhancements that are intended to service the needs of both the DDMoRe Foundation Partnership as a whole, and the broader community at large.

The DDMoRe Foundation *Design Principles*:

Although the DDMoRe Foundation has been established to maintain and enhance content delivered by the DDMoRe Consortium, the DDMoRe Foundation follows a very distinct set of design principles which are compatible with its stated purpose.

Table 1 DDMoRe Foundation Design Principles

Design Principle	Realization of Principle	Implication for DDMoRe Foundation
Sustainable	Able to maintain and grow both standards and infrastructure for the benefit of the global community over time	The exchange standards need to be adopted by the community in order to be viable and become vital. Future infrastructure developments, beyond those created by DDMoRe, need to embrace these standards. DDMoRe Foundation has a role in increasing awareness and encouraging adoption.
Representative	Of a broad range of organization categories within the global community	The DDMoRe Consortium was EU centric whereas the DDMoRe Foundation has to be global in outlook. In the start-up phase of the DDMoRe Foundation, industry and academic organizations will be invited to become partners. Following a successful completion of the start-up phase, other organizational types (Regulatory Agencies, CROs, Scientific Societies, Journals etc.) and Individual Contributors will be invited to enter into partner agreements with the DDMoRe Foundation.
Easily accessible	Organizations can easily become DDMoRe Foundation Partners and derive benefit from both the public domain and DDMoRe Foundation Partner specific content/output	Active management of the "blend" of public domain and partner specific benefits of DDMoRe content and products will be a constant theme for the DDMoRe Foundation Board and the Global Foundation Partnership. The Global Foundation Partnership will assist in setting the priorities of the Foundation year on year at the Annual General Assembly of Partners meeting.
Financially viable	Able to generate sufficient revenue to cover costs	Maintenance of public domain content will have associated costs (hosting, queries, bug fixes etc.). Update and developments to either public domain or partners' specific benefits will also have resource/cost implications. The DDMoRe Foundation is required to generate sufficient revenue to cover the costs associated with Global Foundation Partners ambitions

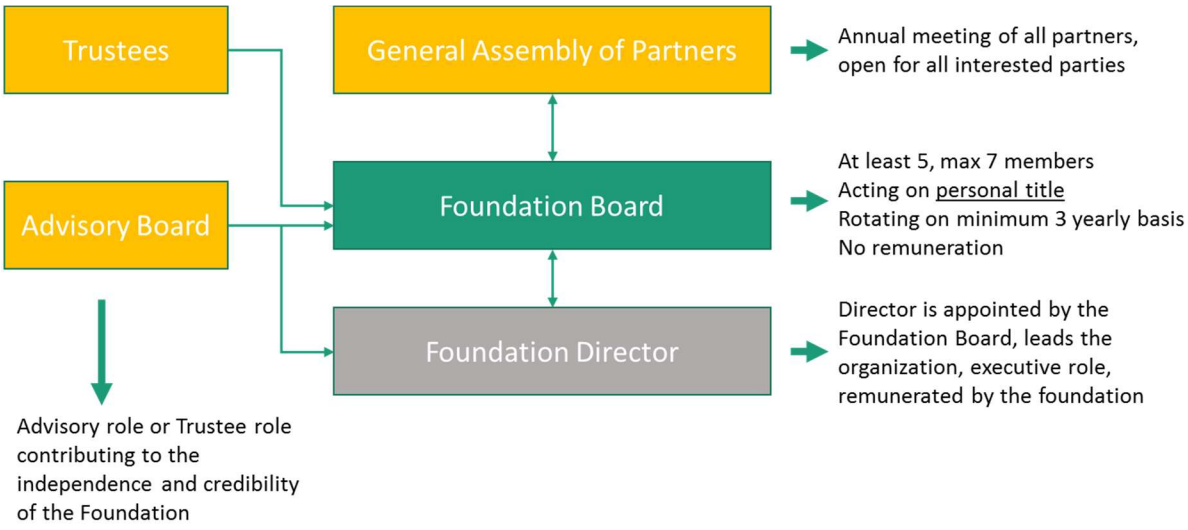
Not for profit	Reinvesting profit in maintaining and improving standards and infrastructure for the community	This is an important feature of the DDMoRe Foundation as it will it will facilitate its ability to be representative of and service the interest of a broad range of organizational types. It is also unambiguous for any resource or content contributor what the motivation of and the delivery priorities of the DDMoRe Foundation are and will be.
Not competitive	Not a competitor for commercial suppliers, but seeding competition to improve tools for the community	The DDMoRe Foundation will lobby, leverage and motivate for enhancement and improvements that benefit the Global Foundation Partners. These enhancements may be manifest as tools emanating from academic foundation partners or commercial suppliers (who provide foundation partners favourable terms of use).
Independent	Autonomous, not relying on financing from, or viewpoint of a particular institution(s)	The DDMoRe Foundation seeks to unambiguously represent the interests of the Global Foundation Partnership. The agreed priorities for the DDMoRe Foundation Partners should be enacted without limitations, bias or conflicts of interest
Efficient	"Lean and mean" organization, able to make and act on decisions	The DDMoRe Foundation will strive to keep organizational overheads to a minimum in order to reduce running costs and facilitate efficient and effective decision making

The DDMoRe Foundation *Organizational Structure*:

a) DDMoRe Foundation Governance and Strategic Level organization

The Board is the governing body of the DDMoRe Foundation and will decide on actions and priorities. The Board is currently composed of Marylore Chenel, Lutz Harnisch, Mats Karlsson, Paolo Magni and Peter Milligan. The composition of the Board, now and in future, will be compatible with the stated aims of the DDMoRe Foundation and its design principles. As shown in Figure 2, the board will eventually appoint a Director, who will responsible for the day-to-day operations of the DDMoRe Foundation. The Director will be appointed when the DDMoRe Foundation is able to cover the costs of an employee. In the start-up phase, and in the absence of a Foundation Director, the DDMoRe Foundation Board will receive day-to-day business support from Hands4Grants and Lygature.

Figure 2. DDMoRe Foundation Governance and Strategic Level organization



Also shown in Figure 2, the DDMoRe Foundation Board will enact additional groups to inform, advise and ensure that DDMoRe Foundation priorities are compatible to the desires of the Global Foundation Partnership and consistent with the DDMoRe Foundation remit:

- Advisory Board: where deemed necessary special interest groups will be instituted to provide the DDMoRe Foundation Board relevant domain insight, review and guidance. The DDMoRe Foundation Board will appoint a chairman for the Advisory Board and in the first instance, Meindert Danhof has agreed to chair these special interest groups.
- General Assembly of Partners: The DDMoRe Foundation will hold an annual meeting to which all Partners are eligible to attend. The meeting will be in large part a scientific gathering where progress against the DDMoRe Foundation goals will be presented by the DDMoRe Foundation Board/Director and partners can vote on the priorities for the DDMoRe

Foundation in the subsequent year. The assembly will also serve as a networking opportunity for the Global Foundation Partnership.

- Trustees: As the DDMoRe Foundation generates both public domain and Partner specific content and influence, trustees can be appointed to represent the interest of the broader community at large and thereby influence the direction of the DDMoRe Foundation.

b) DDMoRe Foundation Operation and Execution Level organization

In accordance with the DDMoRe Foundation design principles the direct staffing level of the DDMoRe Foundation will be small, with one person potentially adopting several roles. Contributions to tasks and services will be achieved through a variety of means including “in-house” DDMoRe Foundation resources, contracted service providers, benefit in-kind contributions and pro bono contributions from interested parties. The proposed operational and execution level organisation of the DDMoRe Foundation is shown in Figure 3. The principle remit of each of the roles, with an estimate of the FTE required during and following the "start-up" phase necessary to service these roles is outlined in Table 2.

Figure 3. DDMoRe Foundation Operation and Execution Level organization

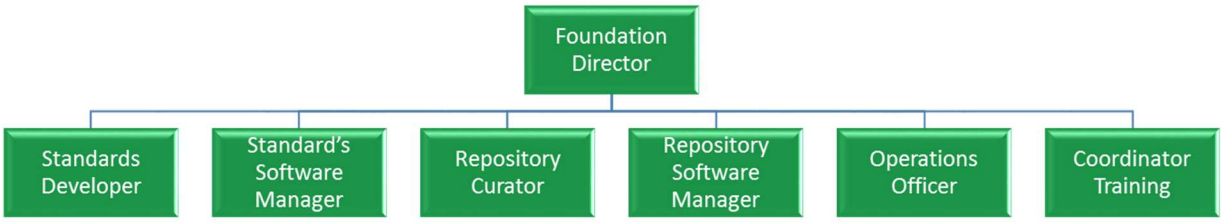


Table 2. DDMoRe Foundation Operation and Execution Level roles and responsibilities

Role	Principal Responsibilities of Role	FTE during "start-up" phase	FTE following "start-up" phase
Foundation Director	Implements the DDMoRe Foundation Boards' strategic plans. Responsible for leadership of the DDMoRe Foundation, its (direct and indirect) staff and outreach and business development. Seeks legal counsel, when necessary.	0.4	0.5
Standards Developer	Creation and coordination of the work groups for maintaining and enhancing each exchange standard documentation and associated artefacts such as XML Schemas.	0.05	0.25
Standard's Software Manager	Maintains and develops the tools and systems associated with the exchange standards. Where necessary distributes work and manages contractors, academic and pro bono contributions. Gap analysis and setting up DDMoRe Foundation software environment, Maintaining and fixing IOF (converters, DDMoRe R package). Product support and hosting.	0.4	0.5
Repository Curator	Responsible for managing the repository content curation process. Develops and maintains SOPs for model curation and qualification. Carries out curation and may contract it out.	0.05	0.25
Repository Software Manager	Responsible for the DDMoRe Foundation's web presence including the running of the model repository. Develops and maintains the repository software and its associated ontological annotation framework.	0.05	0.25
Operations Officer	Day to day running of the office, process, administration, accounting, legal, project management and finance including partner agreements, service provider agreements. Helpdesk installation, meeting organization, communications across all relevant platforms.	0.4	0.5
Coordinator Training	Responsible for development of the range of online training materials and F2F training courses scheduling, advertising organising and leading training. Coordination product archive/service/training, Building training curriculum with academia partners.	0.05	0.25

The DDMoRe Foundation *Partner Contributions*:

As specified in Table 1, the DDMoRe Foundation should appeal to the broad quantitative community, however during the start-up phase the foundation will initially seek partnerships with pharmaceutical and academic institution/organizations. Following a successful completion of the start-up phase, other organizational types including Regulatory Agencies, CROs, Scientific Societies, Journals and individual contributors will also be invited to enter into DDMoRe Foundation Partner agreements.

a) Pharmaceutical Industry Partners:

For the 2016/2017 intake, a minimum of four industrial partners are required to successfully complete the "start-up" phase of the DDMoRe Foundation. Should greater than six companies become DDMoRe Foundation Partners a form of tiered pricing can be introduced.

- *<4 industrial partners:* the DDMoRe Foundation is not viable in the proposed form
- *4 – 6 industrial partners:* each partner contributes €100k
- *>6 industrial partners:*
    - for major companies* - each partner contributes €100k
    - for mid and other companies* - each partner contributes €75k

Companies that become DDMoRe Foundation Partners in 2016/2017 intake will be eligible for a 20% reduction in their contribution for this and subsequent years if a 3 year commitment is provided.

b) Academic Institution Partners:

A minimum of four academic partners are required to successfully complete the "start-up" phase of the DDMoRe Foundation. The requested contribution from each academic partner is a *benefit in kind* contribution of 0.2 FTE.

There is a range of potential *in kind* contributions that can be provided, subject to agreement with the DDMoRe Foundation Board, such as:

- Development and provision of training to DDMoRe Foundation Partners
- Contributions to the Model Review Group (MRG)
- Support for DDMoRe Foundation Partner modelling encoding using DDMoRe standards
- Submission of MDL/PharmML or Certified models to the Model Repository
- Development and Testing of DDMoRe products
- Service Provisions for Software or Methodological development

**Major Companies are defined as those spending ≥US$ 2 billion on ethical pharmaceutical R&D. Mid and Other Companies are defined as those spending <US$ 2 billion in 2015 on ethical pharmaceutical R&D*

Reference: Criteria adopted by CMR International Pharmaceutical R&D Fact book, a Thomson Reuters business.

The DDMoRe Foundation *Expenditure:*

The following tables illustrate the proportion of overall expenditure anticipated for each DDMoRe Foundation role introduced in Table 2.

Table 3 (encompasses the "start-up" phase of the DDMoRe Foundation) and Table 4 (encompasses Phase 2 of the DDMoRe Foundation following a successful completion of the "start-up" phase). The breakdown of the anticipated expenditure is illustrated assuming € 400, 600 or 800K will be raised from financially contributing partners.

These figures represent the overall costs of fulfilling a particular role and do not solely represent salary/labour costs. Furthermore the proportion of overall expenditure associated with each role, under the different scenarios, is intended to illustrate where the DDMoRe Foundation Board sees the priorities and needs for DDMoRe Foundation currently. The DDMoRe Foundation Board has the remit to decide on actions and expenditure priorities in the light of the total contributions obtained in any given financial year and it will do so in accordance with the DDMoRe Foundation Design Principles and its interactions with DDMoRe Foundation Partners.

Table 3. Projected Expenditures during "start-up" phase of DDMoRe Foundation

Role	Expenditures following €400K revenue	Expenditures following €600K revenue	Expenditures following €800K revenue
Foundation Director	0	0	0
Standards Developer	15	25	35
Standard's Software Manager	155	255	355
Repository Curator	10	15	20
Repository Software Manager	15	35	65
Operations Officer	180	225	250
Coordinator Training	25	45	75

Table 4. Projected Expenditures following "start-up" phase of DDMoRe Foundation

Role	Expenditures following €400K revenue	Expenditures following €600K revenue	Expenditures following €800K revenue
Foundation Director	100	120	140
Standards Developer	30	45	60
Standard's Software Manager	80	150	220
Repository Curator	25	40	50
Repository Software Manager	30	45	60
Operations Officer	100	150	200
Coordinator Training	35	50	70

During the "start-up" phase the responsibilities of the DDMoRe Foundation Director will be performed by the DDMoRe Foundation Board. The proportions of expenditures in this phase are a consequence of transitioning legacy DDMoRe Consortium content to enable the first foundation supported product releases and establish the DDMoRe Foundations ability to operate. Appendix 1 illustrates the DDMoRe Foundation Boards proposals to transition and develop relevant content and deliverables from the DDMoRe Consortium into the DDMoRe Foundation. Appendix 2 describes the current status of the DDMoRe products and any necessary activities to permit the first foundation supported product releases.

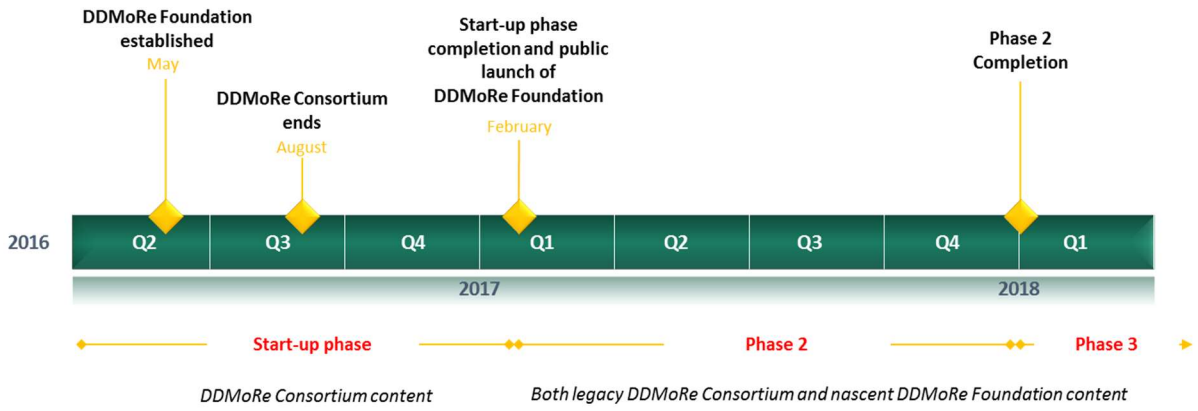
During Phase 2 a DDMoRe Foundation Director will be appointed and there will be a shift of emphasis from transitioning existing products and content to maintaining the legacy content and growing and enhancing relevant DDMoRe Foundation products, content and activities.

The DDMoRe Foundation *Timelines*:

The DDMoRe foundation was established as a Dutch 'Stichting'* in May 2016. Figure 4 illustrates the timeframe of phases that the DDMoRe Foundation board envision to a) transition and develop relevant content and deliverables from the DDMoRe Consortium into the DDMoRe Foundation and b) deliver additional content that is considered important for the Global Foundation Partnership.

The "start-up" phase, ending February 2017, will focus on condition a) set out above. Phase 2, following the successful completion of the "start-up" phase, will focus on condition b) and Phase 3 will be subject to a new set of priorities that will be set out in the 2017/18 invitation document next year.

Figure 4. The DDMoRe Foundation Timelines



The emphasis of this document is the "start-up" phase, and the DDMoRe Foundations Boards strategy to successfully navigate this phase. Appendix 1 illustrates the DDMoRe Foundation Boards proposals to transition and develop relevant content and deliverables from the DDMoRe Consortium into the DDMoRe Foundation.

The assumption is made that the DDMoRe Foundation achieves its minimum level of partner enrolment (4 industry and 4 academic institutions) and it is this level of "early adopter" resource that prosecute and sustain the activities laid out in Appendix 1. Should partner enrolment be greater than this minimum, there will opportunities to advance the proposed Phase 2 activities sooner (and to a greater breadth and depth) consistent with the DDMoRe Foundations' design principle to "reinvest all profit in maintaining and improving standards and infrastructure for the community".

** A "Stichting" (foundation) is a Dutch legal entity with limited liability, but no members or share capital, which exists for a specific purpose. This form of entity makes it possible to separate functions of ownership and control. It is created through a legal act. This act is usually a notarised deed that contains the articles of the foundation which must include the first appointed board. A foundation is governed and represented by a board that is responsible for the foundation's administration.* https://en.wikipedia.org/wiki/Stichting

Appendix 1. Detailed Catalogue DDMoRe Components and emphasis of DDMoRe Foundation during "Start-Up" Phase:

DDMoRe Components	Description of deliverable (black text) or task (coloured text)	Available to Public	Available to Partner	Some DDMoRe Foundation activity during start-up phase?
Standards				
MDL version 1.0	Model Description Language - user readable modelling language	Public		Yes
PharmML version 0.8.1	Pharmacometric Markup Language - a machine readable XML language design to exchange models	Public		Yes
LibPharmML	libPharmML is Java API that provides a convenient way to read, create, write and validate PharmML files	Public		Yes
PKMacro translator	Specific feature of libPharmML	Public		Yes
SO	Standard Output - the standard for capturing output from M&S tools in a consistent way	Public		Yes
LibSO	libSO is Java API to read, write and validate Standardised Output files	Public		Yes
ProbOnto	ProbOnto – and ontology and knowledge base of statistical distributions	Public		
	Setup development infrastructure		Partner	Yes
Model Repository (MR)				
Public instance Model Repository	A public resources for the community to store and share models based on Jummp	Public		Yes
Partner instance + RDF store documentation	Guidelines for a private resource for internal instance to store and share models	Public		Yes

DDMoRe Components	Description of deliverable (black text) or task (coloured text)	Available to Public	Available to Partner	Some DDMoRe Foundation activity during start-up phase?
Metadata framework ReSCU	Total description of the metadata framework	Public		
RDF store	Storing ontology data as RDFs in Virtuoso Open Source edition	Public		Yes
RDF store service	Rdfstore 2.0 & OWLKB 2.0	Public		Yes
LibMetadata	libMetaData extracts information from the RDF Store about what properties should be used to annotate a model and organises it in a way that makes it easy for the Repository to produce the annotation editor.	Public		Yes
LibAnno	LibAnno to validate the annotations entered by users and to assess whether a model matches the minimal requirements for publishing or not. LibAnno also facilitates the process of reading and writing the RDF Statements which represent the machine-processable equivalent of what the user has entered through the annotation editor.	Public		Yes
Annotation tool	Annotation Editor dependent on both libMetadata and libAnno	Public		Yes
Model Qualification Procedure	Generic qualification procedure to certify models in the DDMoRe Model Repository	Public		
	Set-up and Internalization MR		Partner	Yes
	Harmonization MR		Partner	Yes
	Prioritised set of missing features		Partner	Yes
	Development high priority minor elements		Partner	Yes
	System Test and Deployment		Partner	Yes
	First foundation supported release		Partner	Yes
	First foundation supported release documentation		Partner	Yes

DDMoRe Components	Description of deliverable (black text) or task (coloured text)	Available to Public	Available to Partner	Some DDMoRe Foundation activity during start-up phase?
	Logistics Model Review Group		Partner	Yes
Interoperability Framework (IOF)				
MDL definition library	Model Description Language definition library and plug-in to MDL-IDE	Public		
MDL editor	Editor for Model description language and plug-in to MDL-IDE	Public		Yes
MDL-IDE	MDL-IDE provides MDL editing and validation, but no tool execution including the MDL to PharmML converter as a stand-alone module within MDL-IDE that generated PharmML code from MDL code.	Public		Yes
CCoPI-mono (CM)	Lighter version of the common converter	Public		Yes
PharmML->NM-TRAN Converter	Converter PharmML to NM-TRAN, using CM	Public		Yes
PharmML->WinBUGS Converter	Converter PharmML to WinBugs, using CM	Public		Yes
PharmML->PFIM Converter	Converter PharmML to PFIM, using CM	Public		Yes
PharmML->MLXTRAN Converter	Converter PharmML to MLXTRAN, using MLXLibrary	Public		Yes
PharmML->PopED Converter	Converter PharmML to POPED, using C++	Public		Yes
PharmML->MATLAB Converter	Converter PharmML to Matlab	Public		
NM-TRAN -> MDL converter	NM-TRAN to MDL conversion script		Partner	Yes
PharmML->MDL	Converter from PharmML -> MDL	Public		

DDMoRe Components	Description of deliverable (black text) or task (coloured text)	Available to Public	Available to Partner	Some DDMoRe Foundation activity during start-up phase?
NONMEM Connector	Uses interoperability framework to sequence conversion from PharmML-> NMTRAN, execution with NONMEM, conversion of NONMEM output to Standard Output (SO) object and return as R object.	Public		
Monolix connector	Connector to Monolix	Public		Yes
WinBUGS Connector	Connector to WinBugs depending on CM	Public		
PsN Connector(s)	Connector for PsN performing PsN tasks on NMTRAN converted models.	Public		
Simcyp SO Generator	Connector to Simcyp depending on Simcyp Simulator platform under SIMCYP License	Public		
Monolix SO Generator	Monolix SO generator	Public		
WinBUGS SO Generator	WinBugs SO generator	Public		
nmoutput2so	Converter from NONMEM output to standard output. Used by the NONMEM and PsN connectors	Public		Yes
Libsoc	Converter from PopED output to standard output	Public		
DDMoRe R package	R scripts to execute models in target languages	Public		Yes
Standalone Execution Environment (SEE)	Standalone Execution Environment for Interoperability Framework	Public		
Standalone Execution Environment (SEE) Installer	Installer Standalone Execution Environment for Interoperability Framework	Public		
Framework Integration Service (FIS)	Framework Integration Service for Interoperability Framework	Public		

DDMoRe Components	Description of deliverable (black text) or task (coloured text)	Available to Public	Available to Partner	Some DDMoRe Foundation activity during start-up phase?
Converter Toolbox Service (CTS)	Converter Toolbox Service for Interoperability Framework	Public		
Task Execution Service (TES)	Task Execution Service for Interoperability Framework	Public		
	Set-up and Internalization IOF		Partner	Yes
	Test and evaluate rebuild IOF		Partner	Yes
	Harmonization IOF		Partner	Yes
	Prioritised set of missing features		Partner	Yes
	Development high priority minor elements		Partner	Yes
	System Test and Deployment		Partner	Yes
	First foundation supported release		Partner	Yes
	First foundation supported release documentation		Partner	Yes
	Amazon instance of IOF		Partner	Yes
Workflow (WF)				
Workflow Framework Infrastructure	Tools for making an organisation "workflow aware" - integration with task execution and version control systems, to generate events initiated by the user, in order to make workflow as seamless as possible. Also responsible for performing re-execution / rerun.	Public		
Workflow client	Desktop/web client for querying the workflow datastore, and visualising the results. Rerun may be initated from here. Also will provide mechanisms to set states for models, e.g. pivotal or QC'ed.	Public		
Workflow R package	R package for querying workflow datastore and visualising the results. Support for interaction with the local file system and	Public		

DDMoRe Components	Description of deliverable (black text) or task (coloured text)	Available to Public	Available to Partner	Some DDMoRe Foundation activity during start-up phase?
	repository, and creating relationships between models (clone etc.)			
Workflow datastore	Storing thoughtflow information - model evolution/progression, tasks executed, (inputs to outputs) and information relating to the model development process (comments, model states, etc.)	Public		
	Set-up and Internalization WF		Partner	Yes
Training				
Online training materials		Public		Yes
	Set-up and Internalization Training		Partner	Yes
	Prioritised set of missing features		Partner	Yes
	Design DDMoRe product training		Partner	Yes
	Accreditation DDMoRe		Partner	Yes
Outreach				
ddmore.eu		Public		Yes
PharmML.org		Public		
ProbOnto.org		Public		
	Creating tools for building User base	Public	Partner	Yes
	Website ddmore.org	Public		Yes
	ACOP meeting	Public		Yes
	Promotion materials early adopters	Public	Partner	Yes
	First annual DDMoRe foundation meeting	Public	Partner	Yes
DDMoRe Foundation				

DDMoRe Components	Description of deliverable (black text) or task (coloured text)	Available to Public	Available to Partner	Some DDMoRe Foundation activity during start-up phase?
office				
	Early adopters contracts		Partner	Yes
	DDMoRe Foundation staff contracts		Partner	Yes
	Accounting		Partner	Yes
	Legal support		Partner	Yes
	Project Management		Partner	Yes

Appendix 2. Current Status of DDMoRe Products:

The DDMoRe Consortium products have been delivered into the public domain, and it is the task of the DDMoRe Foundation to evaluate and optimize these products in the light of its design principles.

Exchange Standards

The foundation considers the exchanges standards (MDL, PharmML, SO) of sufficient quality and content to be ready for incorporation into the first foundation supported release. MDL version 1.0, PharmML 0.9, SO 0.3, ProbOnto 2.0

Model Repository

The public domain Model Repository is available to upload models in any original target tool code, MDL and PharmML. Models can be annotated to improve the search functionality and certification for models can be requested. The repository is hosted and maintained by the DDMoRe Foundation for public use at http://repository.ddmore.eu/ . DDMoRe Foundation Partners can obtain a private instance of the Model Repository which has been tested and evaluated in a Pharmaceutical Industry setting.

Although the Model Repository is a mature product it currently does not display models which use the latest version of PharmML. Also the full set of annotations provided in the Metadata Framework has not been fully implemented. During the start-up phase these factors will be addressed such that an enhanced version of the Model Repository can be included in the first foundation supported release.

Interoperability Framework

The Interoperability Framework utilizes the exchange standards, to enable efficient integration of models, and the associated outputs, across modelling languages for existing and new tools. It currently supports the following target tools; NONMEM, MONOLIX, PsN, PFIM, PopED and WinBugs and it can be downloaded as a stand-alone version (SEE). It will be necessary for the DDMoRe Foundation to refine and re-build the Interoperability Framework in its own environment to address outstanding quality matters and improve the product, before forming part of the first foundation supported release.

A server version of the Interoperability Framework has been successfully implemented and tested within a Pharmaceutical Industry setting (Novo Nordisk, Novartis, Servier) as a proof of concept. This version has been delivered with an earlier version of the Interoperability Framework and will require to be upgraded with the latest version of the SEE. In addition, the foundation has identified architectures that enable an alternative version of the Framework to be produced that simplifies and minimises the product implementation overhead.

Training

Training material for a range of DDMoRe Products are available online in the form of tutorials and will be completed with the use-cases obtained from the DDMoRe training courses. The training material derived from the range of courses delivered during the lifespan of the DDMoRe Consortium can be adapted to form specific DDMoRe Foundation product courses. These courses will form part of the first foundation supported product release.

The foundation will also consider investment in a tailored training program showing the benefit of DDMoRe products in the setting of MID3. Such a training programme would be contingent on successful completion of the “start-up” phase and the level of priority DDMoRe Foundation Partners would give to such and investment of resources.