



Kick-off meeting to initiate Community Groups

Stuart Moodie - Eightpillars, Wendy Aartsen – Hands4Grants, Mike Smith - Pfizer,
Celine Sarr - Pharmetheus, Justin Wilkins - Occams,

Objective of the meeting



- Introduce the presenters and audience (2 min)
- Introduce DDMoRe foundation (15 min)
 - Products status as they are now
 - Its vision
 - Its objectives
 - Community engagement
- Introduce community groups (10 min each)
 - **Why they have been created?**
 - **What will be their focus?**
 - **How individuals can contribute to them?**
- **Discussion (13 min)**

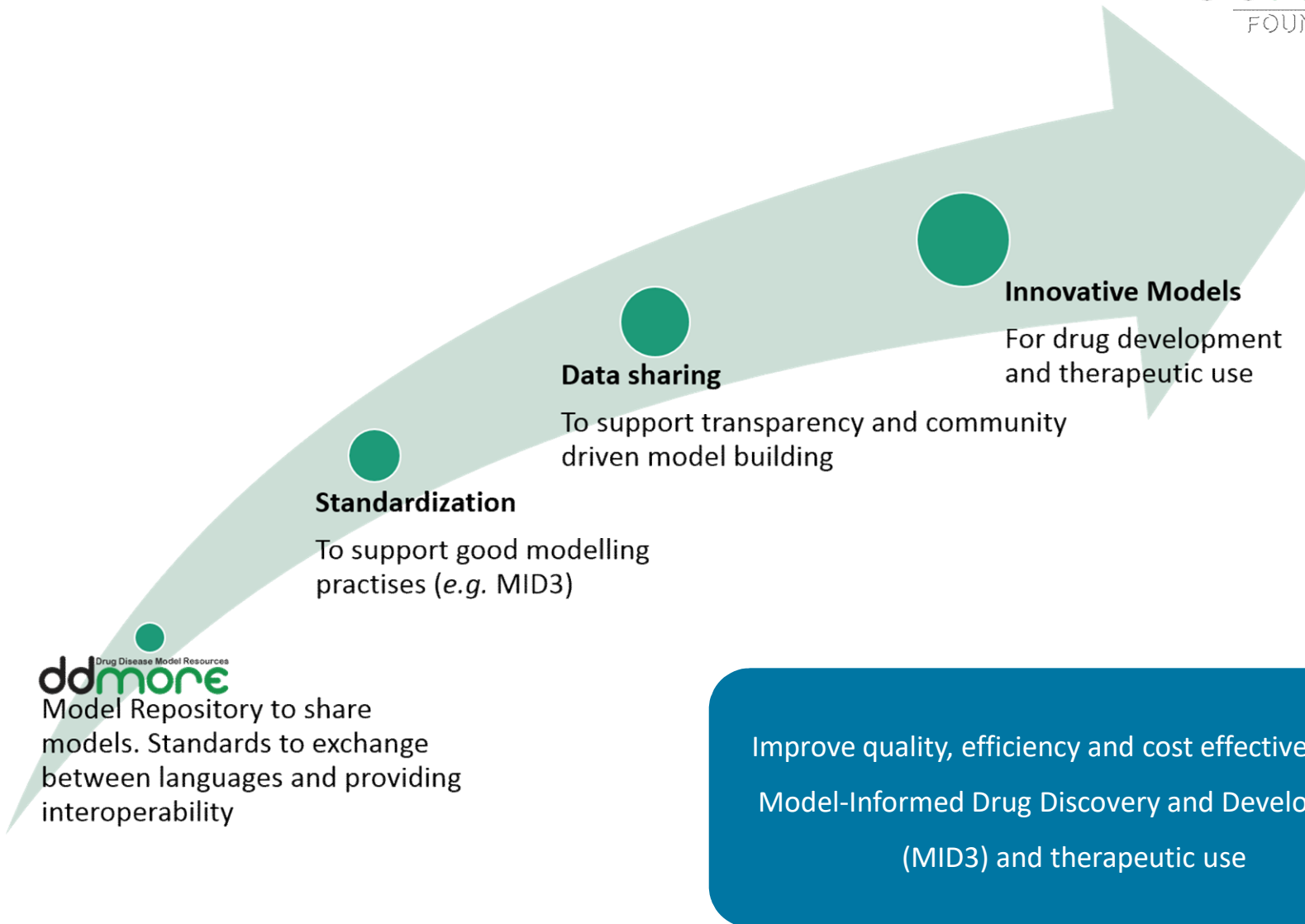
Audience



- We like to know who you are
- We like to know your relation to DDMoRe
- We like to know your scientific interests and experiences
- We like to know your motivation

In order to obtain a starting profile of the audience attending today or in the future, we will ask you to complete the final questions of the survey <https://nl.surveymonkey.com/r/XS7HGR5>
This will make it easier to exchange information and to tailor information to the needs of the audience.

DDMoRe foundation vision



DDMoRe Foundation objectives



Advocate

and contribute to the development of
common standards

Facilitate

uptake of new methodologies
model sharing and model transparency

Support

model-informed
decision making

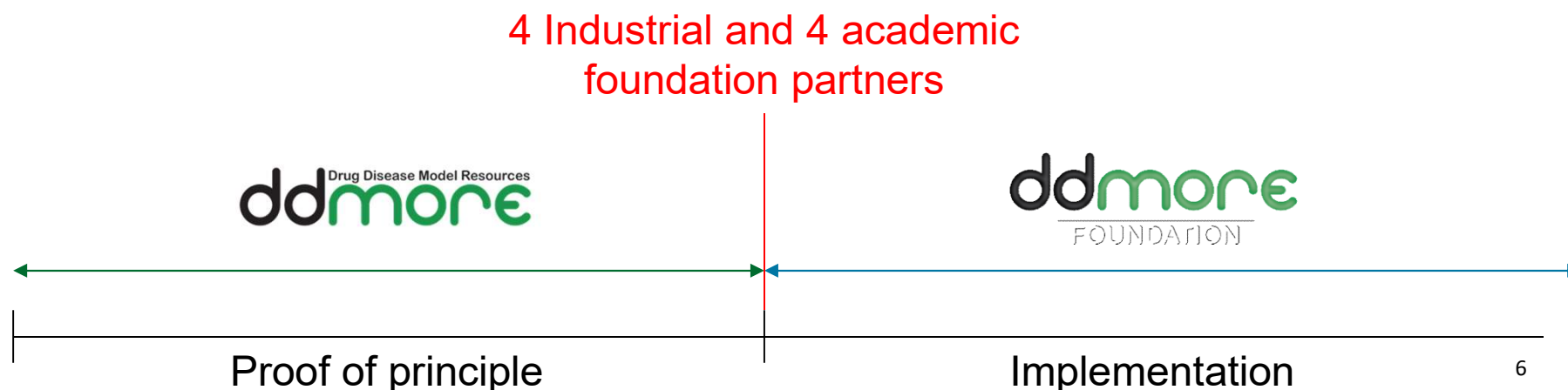
Provide

means for training and education
for use, adoption and awareness

Business plan Foundation



- 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



Why community groups?



- Community Groups are part of the DDMoRe Foundation outreach & engagement strategy
- The aim is to create a continuous interaction/dialogue with the users and contributors of the DDMoRe open-source products
- Listen to the problems and issues raised by users and contributors of the DDMoRe open-source products
- Align with community initiatives
- Ask for feedback on new developments or strategic choices

Join our community groups

ddmore
FOUNDATION

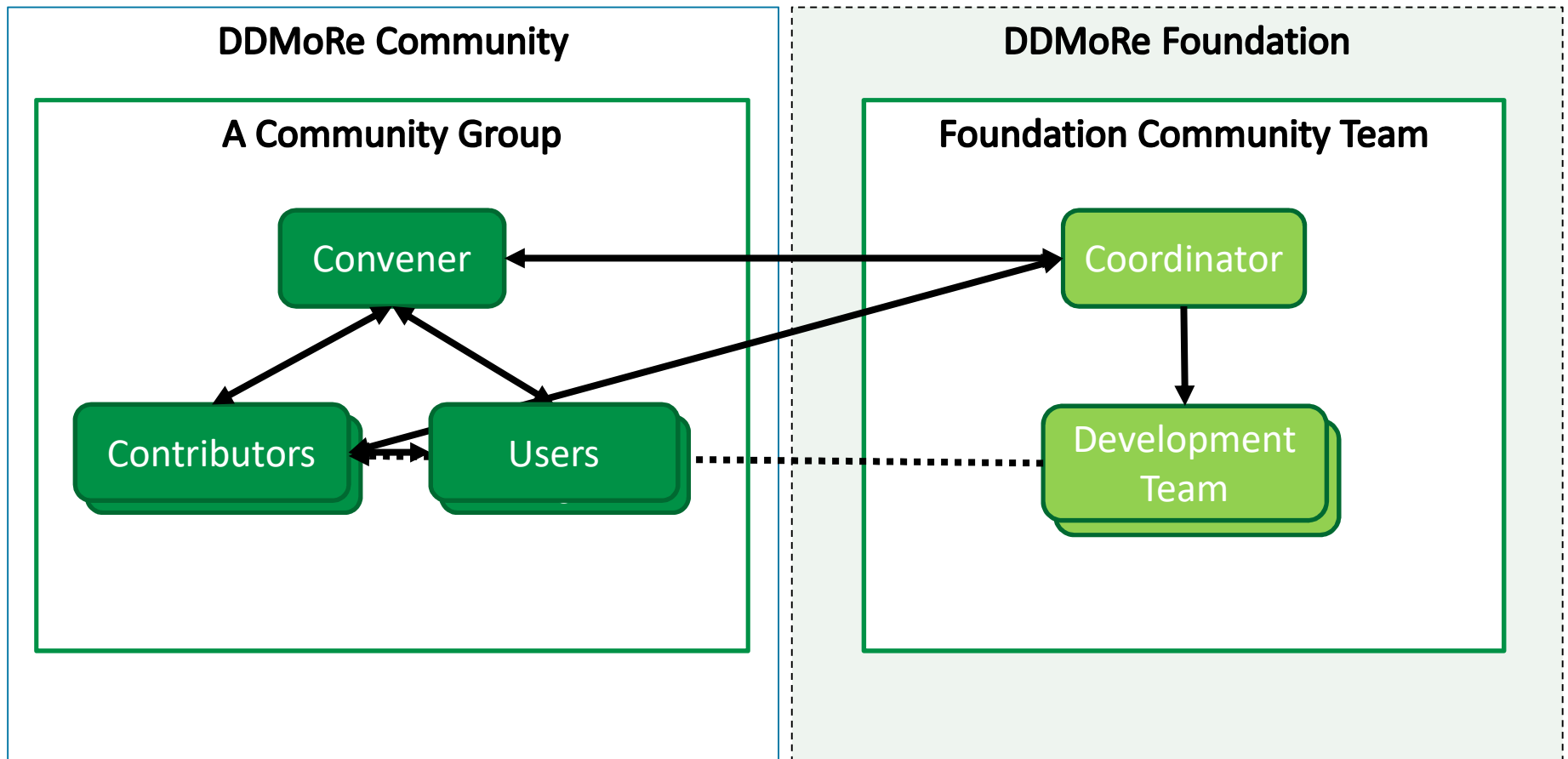


Community Groups characteristics



- A group of **volunteers** with an interest in the vision of the DDMoRe Foundation
 - Model sharing, open standards for model exchange, interoperability tools, provenance and workflow tracking.
- Willing to spend some time (free to define for each person) to serve the community and advance the vision
- Participating actively for the benefit of the group
- Each group will be **actively supported** by the DDMoRe Foundation with project management/communication
- Group actions will be described on the DDMoRe Foundation website as contributions by the community
- Output will be open source and available to all

How are Community Groups structured?



What does the Foundation facilitate?



Provide support for each community group:

- Website, wiki site, forums and mailing lists
- Provide project management and admin
 - Schedule meetings
 - Provide agenda , minutes and structure to the discussions
 - Administer websites, forums etc.
 - Oversee elections, votes or surveys.
- Communication around progress and results
- Continuous feedback to the Foundation Board
- Actively search for new ways of recognition for contributions by community group members

How to engage?

- 17 January 2017: Kick-off TC for all three community groups
 - Languages – Convener: Mike K Smith
 - Model Repository – Convener: Celine Sarr
 - Thoughtflow – Convener: Justin Wilkins
- The Foundation team is led by Stuart Moodie and Wendy Aartsen
- Regular TCs (every 14 days or every month) to be defined for each group
- Subscribe to the distribution list at <https://www.surveymonkey.com/r/XS7HGR5>



DDMoRe Languages

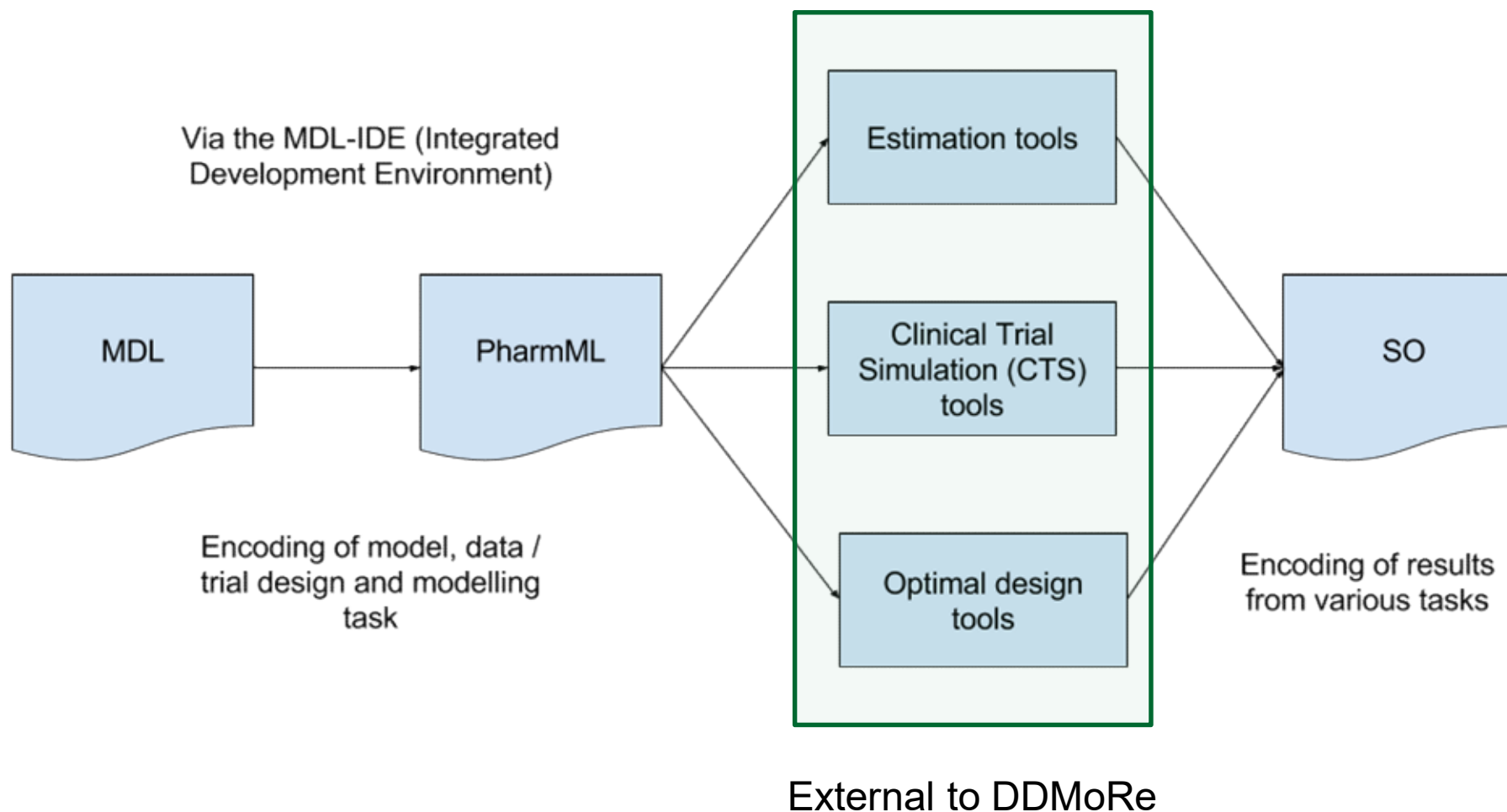
Community group – convener: Mike K Smith - Pfizer

DDMoRe Exchange standards



- Model Description Language (MDL)
 - User-focussed language for expressing models in a target tool-agnostic way.
 - Converts to PharmML for interoperability.
- Pharmacometrics Markup Language (PharmML)
 - Conveys (MDL) models, annotations, information for conversion in a computer-readable language (XML).
 - Probonto knowledge base / ontology of probability distributions.
- Standard Output (SO) object
 - Returns target tool output in a consistent manner (XML)

DDMoRe Exchange standards



DDMoRe Exchange standards



■ Why MDL?

- To allow users to specify models in a consistent language, regardless of the target tool they prefer to use for a given task and consistent regardless of task: estimation, simulation, or optimal design.
- OPEN standard for model description.

■ Why PharmML?

- As the basis for interoperability between target software tools.
- Integrates tools into workflow via standard description of models and inputs.
- Captures metadata, annotations, ontology etc.

■ Why SO?

- To integrate tools into workflow via a standardised output.

Languages group



- Core business – Foundation *with* Community Group
 - MDL, PharmML, Probono, SO specifications
 - Supporting tools (MDL Editor and validator, libPharmML, libSO)

- Derived from core business – Community Group (with Foundation)
 - Interoperability framework tests
 - Interoperability tools
 - Converters
 - Interoperability framework
 - ddmore R package

Languages status

Current features		
MDL : Model Description Language	v1.0	With associated User Guide and Reference manual
PharmML : Pharmacometrics Markup Language	v0.9	PharmML v0.8.1 supported with MDL v1.0
ProbOnto : Probability Ontology / Knowledge Base	v2.0	
libPharmML (Java)	v0.7	Supports PharmML v0.8.1
PharmML SO : Standard Output	v0.3.1	

Gaps	
MDL	Model features not supported: L2, BLQ, Censoring (beyond right censoring for Time to Event), ...
PharmML	Support for PharmML in tools / interoperability framework is limited to v0.8.1.
PharmML SO	Capturing simulation results in SO not tested. Capturing optimal design results in SO -> Feedback to PharmML Design

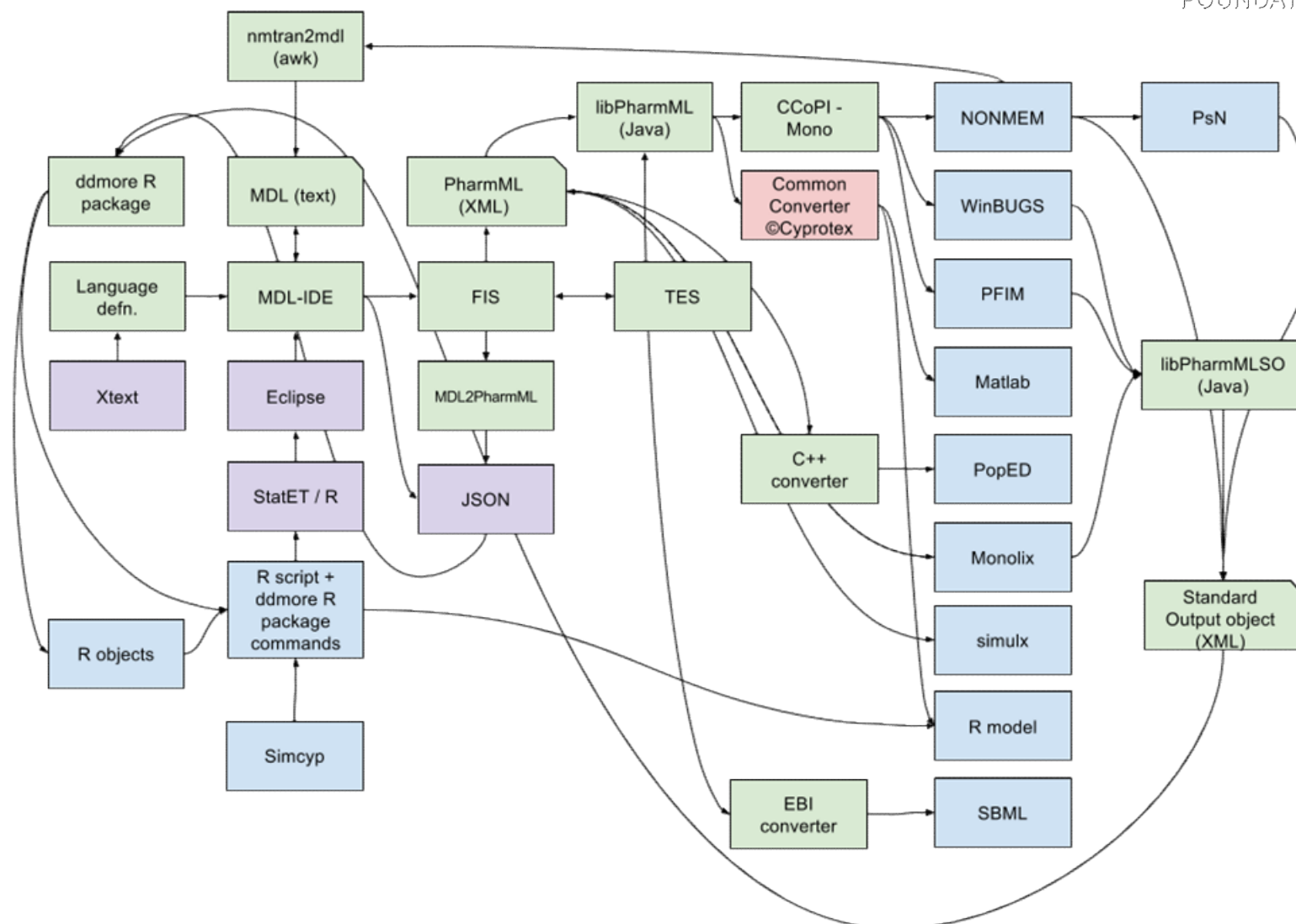
Dia 18

CS8

I think the gaps are understandable for user but not the features.....this are not features these are version number...what about we put features instead?

Celine Sarr, 1/15/2017

Technical landscape



Associated tools status

Currently available – Open Source

libPharmML	PharmML -> NMTRAN	NONMEM -> SO
PKMacro translator	PharmML -> WinBUGS	WinBUGS -> SO
libSO	PharmML -> MLXTRAN	Monolix -> SO
MDL-Editor	PharmML -> PFIM	
CCoPI-mono	PharmML -> PopED	
Infix -> PharmML	PharmML -> Matlab	
ddmore R package		
NMTRAN -> MDL		

Prototype versions – various licenses and states of development

MDL ANTLR4 grammar	PharmML -> R (deSolve)
SBML -> PharmML	PharmML -> C++
SBML -> MDL	PharmML -> Fortran / C
Simcyp connector (call Simcyp using ddmores R functions)	

Languages group

- Roles, skills and tasks:
 - **Mike K Smith** – coordinator of Languages group, MDL subject matter expert (SME).
 - **Stuart Moodie** – DDMoRe Foundation, MDL-Editor, MDL to PharmML SME
 - **Maciej Swat** – PharmML, PharmML SO, ProbOnto SME
 - Various – Conversion tools SME
 - Various –Target software tool SMEs

Languages group

- Steps to implementing new language features:
 1. **Identify** – “What needs to be added?”
 2. **Diagnose / Define**
 1. “In maths / stats / pharmacology / drug development terms, what is the problem that we’re trying to address?” (Provide some example models to illustrate)
 2. Then define MDL
 3. Then define how MDL maps to PharmML
 4. Then how PharmML translates to target software languages
 3. **Discuss / review / refine** – “Let’s review what we’re suggesting...”
 4. **Implement** – “Make changes and evaluate.”
 5. **Document** – “Update documentation to show what was implemented.”

Languages group

■ Foundation's role:

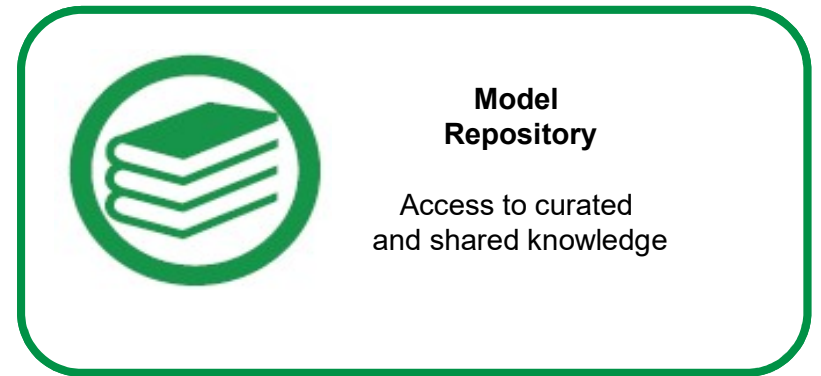
- Manage the standards.
- Oversee strategic direction.
- Ensure that the standards ***come together*** in products e.g. interoperability, repository.
- Promote the use of the standards:
 - Across software developers
 - Through the repository & associated models
 - In discussion with stakeholders (industry, regulatory, businesses)

■ Community role:

- To help steer evolution, development of the languages and associated tools.
- To capitalise on the standards through building / refining converters, interoperability tools.

Lessons from other Standards?

- Standard needs to be driven by community
 - Different fields have different ways.
 - Don't impose too much organisational structure: let it evolve.
- Standards need leadership
 - In practice there are a few engaged and active contributors.
 - Care needs to be taken not to leave the "Quiet minority" behind.
- Standards need money and resources to be sustainable.
 - Web sites
 - Online Forums and mailing lists
 - Meetings and hackathons
- Standards need organisation
 - Contributors are generally more interested in the "fun stuff" than organisation.
 - Need a coordinator to prod the group to meet every month, write minutes, document...
 - Coordinator most likely to coordinate if it's their job!
- Standards need tools
 - A successful standard needs tools and APIs to help it's adoption. Particularly where there is exchange of information.



DDMoRe model repository


Community group – convener: Celine Sarr - Pharmetheus

Introduction

- <http://repository.ddmore.eu>
- How many people in the audience are familiar with the Model Repository?
- For what jobs do you use the Model Repository?
- Why we think the Model Repository has added value
 - Not starting from scratch any more
 - Increase model visibility, model understanding and model review → quality
 - Allow to team-up with colleagues to build models
 - Facilitate internal knowledge storage (private instance)
 - Disseminate innovation and receive scientific recognition
 - Promote standardization via PharmML/MDL
 - Teaching examples

Overview of the tool (1/2)

■ Model listing



Login

BROWSE SUBMIT FEEDBACK

Models

10 20 50

Name	Format	Submitter	Submitted	Modified
Likert Pain Score Modeling: A Markov Integer Model and an Autoregressive Continuous Model	Original code	Anders Thorsted	2016/05/24	2016/05/27
Population PK of gentamicin in cancer patients with time-varying covariates	Original code	Kajsa Harling	2015/12/01	2016/05/26
Nielsen2007_semimech_PKPD_antibiotics	Original code	Anders Kristoffersson	2015/11/30	2016/05/25
Clinical Rifampicin PKPD Model using the Multistate Tuberculosis Pharmacometric Model	Original code	Robin Svensson	2015/11/30	2016/05/25
Chan 2010 - HIV PKPD Viral Load Model	PharmML	Phylinda Chan	2015/12/10	2016/05/25
Benson 2014 - FAAH Inhibitors Systems Pharmacology Model for Pain	PharmML	Phylinda Chan	2015/12/10	2016/05/25
Terranova_2013_oncology_TGI_combo	PharmML	Paolo Magni	2015/12/10	2016/05/24
DelBene_2009_oncology_in_vitro	PharmML	Paolo Magni	2014/09/25	2016/05/24
Rocchetti_2013_oncology_TGI_antiangiogenic_combo	PharmML	Paolo Magni	2014/09/26	2016/05/24
Simeoni_2004_oncology_TGI	PharmML	Paolo Magni	2014/09/25	2016/05/24

Overview of the tool (2/2)

Brief, but descriptive title

Public model

Simeoni_2004_oncology_TGI

OverviewFilesHistoryModel DefinitionEstimation Steps

Model Description:
PKPD model of Tumor Growth Kinetics in xenograft models after administration of anticancer agents

Format:
PharmML (0.6.1)

Related Publication:
[Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents.](#)
Simeoni M, Magni P, Cammia C, De Nicolao G, Croci V, Pesenti E, Germani M, Poggesi I, Rocchetti M
Cancer research, 2/2004, Volume 64, Issue 3, pages: 1094-1101

Contributors:
Paolo Magni

Context of model development:
Candidate Comparison, Selection, Human Dose Prediction;

Model compliance with original publication:
Yes;

Model implementation requiring submitter's additional knowledge:
No;

Modelling context description:
The available mathematical models describing tumor growth and the effect of anticancer treatments on tumors in animals are of limited use within the drug industry. A simple and effective model would allow applying quantitative thinking to the preclinical development of oncology drugs. In this article, a minimal pharmacokinetic-pharmacodynamic model is presented, based on a system of ordinary differential equations that link the dosing regimen of a compound to the tumor growth in animal models. The growth of tumors in nontreated animals is described by an exponential growth followed by a linear growth. In treated animals, the tumor growth rate is decreased by a factor proportional to both drug concentration and number of proliferating tumor cells. A transit compartmental system is used to model the process of cell death, which occurs at later times. The parameters of the pharmacodynamic model are related to the growth characteristics of the tumor, to the drug potency, and to the kinetics of the tumor cell death. Therefore, such parameters can be used for ranking compounds based on their potency and for evaluating potential differences in the tumor cell death process. The model was extensively tested on discovery candidates and known anticancer drugs. It fitted well the experimental data, providing reliable parameter estimates. On the basis of the parameters estimated in a first experiment, the model successfully predicted the response of tumors exposed to drugs given at different dose levels and/or schedules. It is, thus, possible to use the model prospectively, optimizing the design of new experiments.;

Modelling task in scope:
estimation;

Nature of research:
In vivo; Preclinical development;

Therapeutic/disease area:
Oncology;

Validation Status:
Annotations are correct.

Textual description of model

Submitter or Collaborator

Link to Reference
(if existing)

Model annotation (under development)

Model Repository status



Current features

Model entry display, version history, and Annotations display

Model Equations/Parameter values, display PharmML 0.6.1

Model download

Private instance

Manual export of repository content for statistics reporting

Automatic publishing process, automatic annotation checks

Advanced search (syntax- based) including annotations fields and corresponding terms

Robust team management

publication import

Corresponding contextual help

Model Repository Core business

Foundation input



Make the public Model Repository the go-to resource for modellers

We can do this by:

- **Providing a wide range of models**
- **Curating models** so that its content is useful.
- Providing good quality and searchable model annotations
- Integrating with DDMoRe interoperability tools and standards.
- **Improving the user interface** to it is intuitive, reliable and easy to use.
- Providing a secure environment where user's confidentiality and data is safe-guarded.

Foundation's role

- Provides and administers public repository
- Provides software maintenance
- Provides enhancements to repository with input from Community Group
- Priorities for development work set by Foundation Board.

Model Repository

What the community group could focus on?



- We are looking for input from the community:
 - To upload models
 - To curate models
 - To improve the user interface and give feedback for development team
 - To test “private instance” of the user interface
 - To create new networks and channels to populate it (e.g. journals, congresses, sponsorships)
 - To create ways to recognize individual submitters

Model Repository

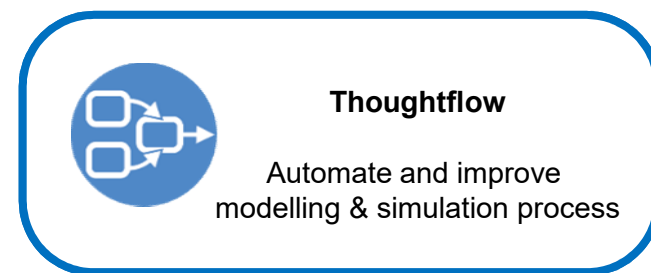
Targets and milestones



- End of Q1 2017
 - Community group set up and regular TCs organized
 - Planning defined with short term tasks and specific responsibilities

- End of Q2 2017
 - Review of the first 6 months of activity
 - Adaptation of the group process if needed
 - Progress status

- The repository will be the priority of the Foundation

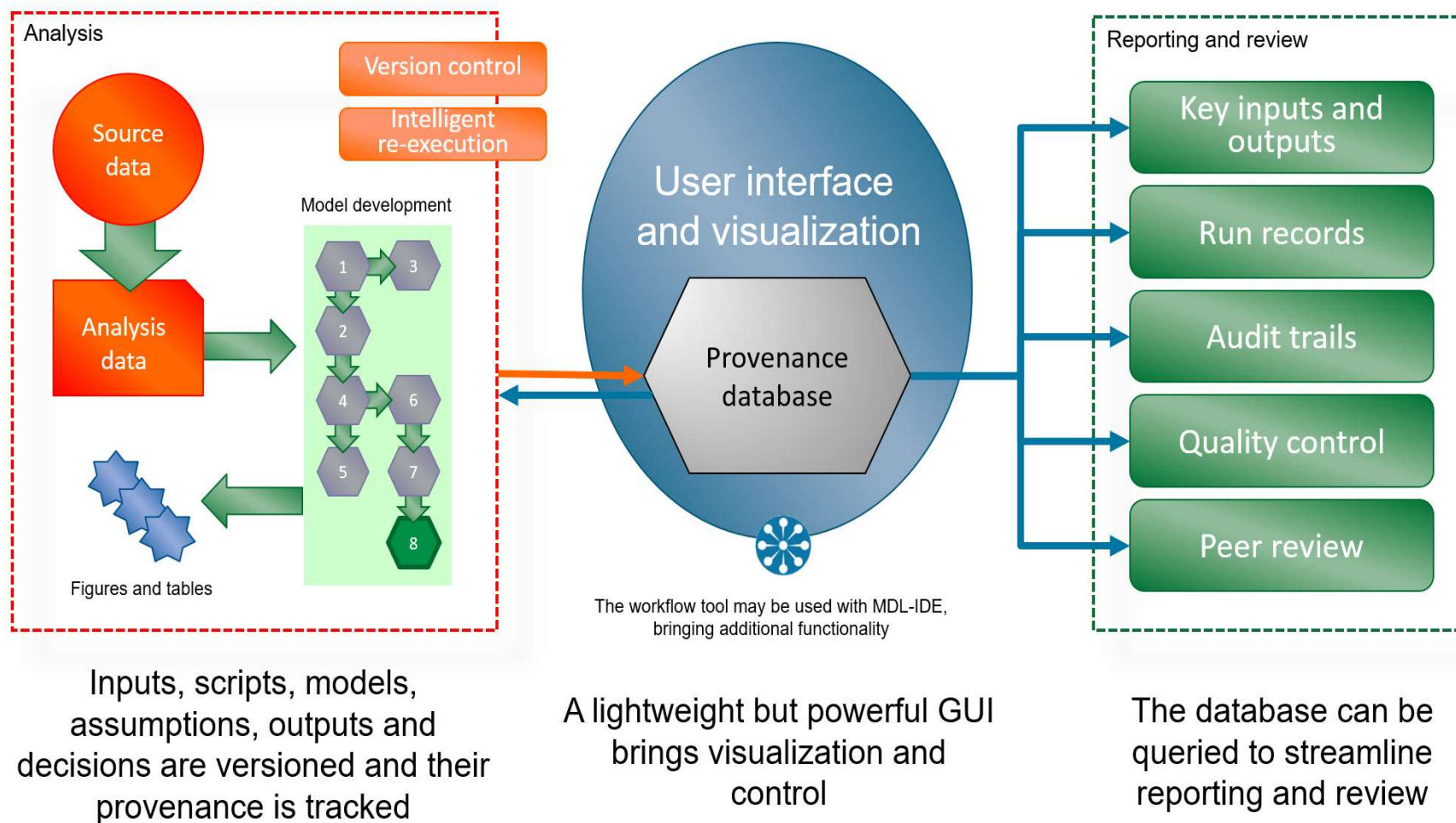


Thoughtflow

Community group – convener: Justin Wilkins - Occams

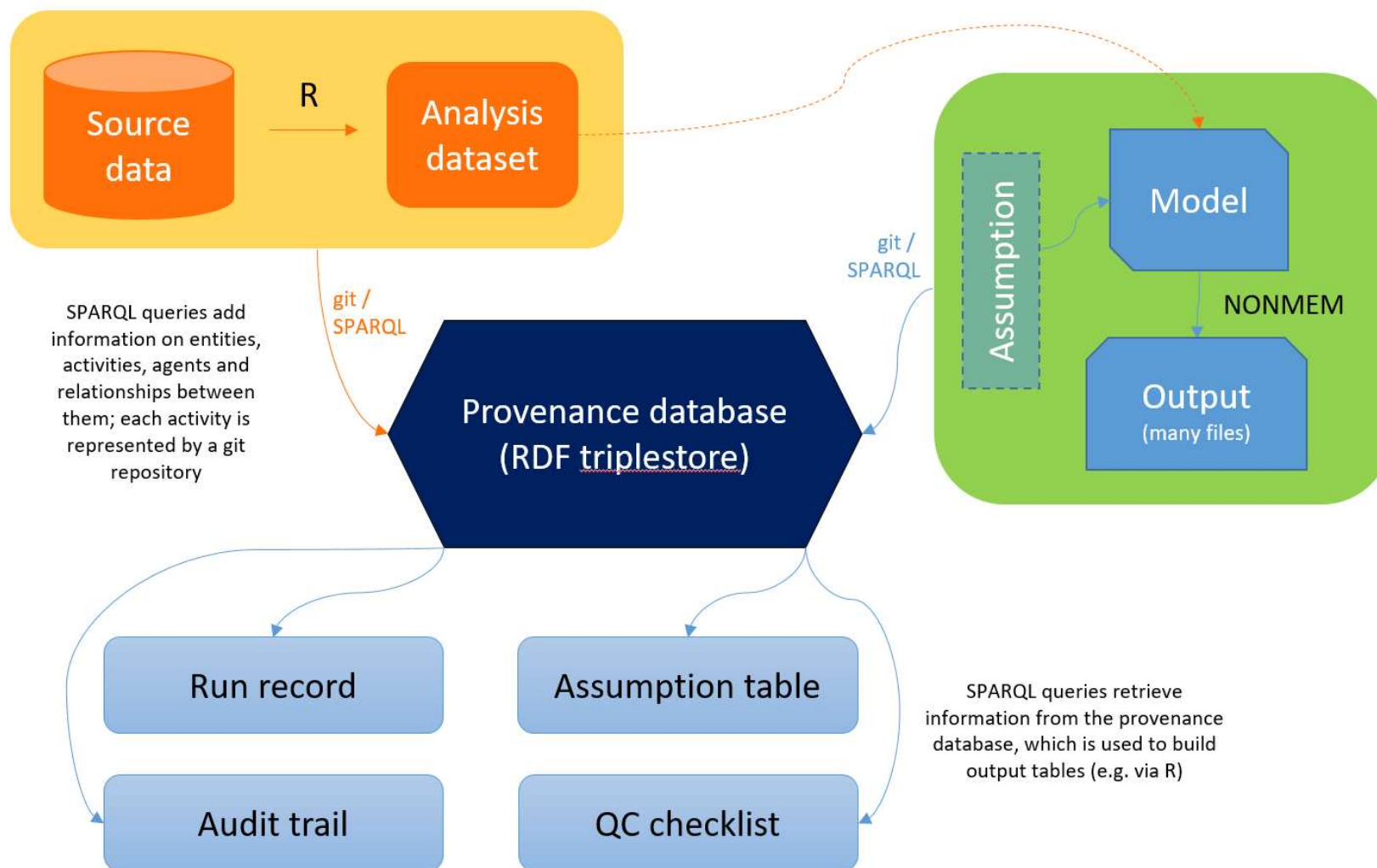
Thoughtflow

Concept



Thoughtflow

A simple example



Thoughtflow

■ Core business

- In the short term, the Thoughtflow Community Group will publish a complete first version of the Thoughtflow ontology and specification
- This would be followed up with free and open source reference implementations and accompanying support tools, leveraging the R ecosystem as much as possible

■ Derived from core business

- Fully qualified production implementations, in the medium to long term

■ Status

- A crude prototype demonstrator, and a draft ontology and specification are available
- A position paper is accepted by peer-reviewed journal CPT: PSP and will be published shortly in Q1 2017

Thoughtflow

- Who do we need?
 - Pharmacometricians who see the value of an open-source workflow tool, to help steer the project, and to help write the documentation
 - Coders who can turn ideas into reality: R, Shiny, Java, ...
 - Any other interested parties with time and enthusiasm
- Budget
 - Enthusiasm for volunteer work that benefits the community (i.e. US\$0)
- Targets and milestones
 - Published ontology and specification (almost there)
 - Beta tool (medium to long term)
 - Production-ready tool (long term)

Next meeting...



- All people in the audience will be asked to complete the survey
- According to the group(s) you have chosen you will receive a Doodle
- Convener will organize the next community group meeting and inform the registered group members

Info



For more information, comments or questions on the DDMoRe Foundation please feel free to contact:

Board Members:

- Marylore Chenel – Servier
- Mats Karlsson - University of Uppsala
- Peter Milligan - Pfizer
- Paolo Magni - University of Pavia

Technical support:

- Stuart Moodie - Eightpillars

Support and advice:

- Herman Verheij - Lygature
- Wendy Aartsen - Hands4Grants

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CS10

we are missing the conveners...

Celine Sarr, 1/15/2017

