

Standards Governance – a First Insight

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Brussels, 15 October 2013

Agenda

- Merck Serono Standards
- People / Roles / Responsibilities
- Process Flow
- General Remarks / Challenges / Conclusion

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Standards Used@Merck Serono

Standard Types

General and Therapeutic Area Data Standards Collection Modules (*)

Merck Serono SDTM Standards (*)

Merck Serono ADaM Standards (*)

Merck Serono Controlled Terminology (*)

Merck Serono Value Level Metadata (*)

GBS Output Standards

Standard algorithms

The official CDISC Standards

Validated standard programs and tools

(*) Subject to Governance Process

Why Standards?

- Implementation of CDISC Standards **mandatory for submissions** to FDA (CDER, CBER)
- **Consistency in submission** packages requires maintenance of Merck Serono Standards
- **Effective use of the Clinical Data Repository** at Merck Serono is based on data standards for SDTM and ADaM
- Further expected standardisation improvements (**reduction timeline + efforts**)
 - re-use of standard programs (e.g. QC checks)
 - reduction of efforts required for adaptations on trial level
 - facilitate review process and communication for FDA submissions
 - improvement for communication with external partners and in staffing

Why SDTM Standards?

- Current CDISC SDTM Standard builds a solid ground
- But....
 - SDTM IG includes implementation **options**, room for interpretation
 - Therapeutic Area Standards are missing to large extent
 - current CDISC Controlled Terminology is not sufficient (but growing)
- Company specific guidelines
 - harmonized approach across projects
 - internal/external communication tool for our requirements
- Internal processes based on SDTM



Merck Serono SDTM Data Model

- Merck Serono SDTM Model consists of (current) 3 different model definitions
 - SDTM Model **Domain**, contains...
 - Each domain in detail including
 - Definition / Listing of all domains specified for the Merck Serono SDTM model. Includes all general and sponsor defined domains and the appropriate dataset level metadata (dataset purpose, key structure etc.)
 - SDTM Model **CT** (Controlled Terminology), contains...
 - Definition / Listing of the Controlled Terminology specified for the Merck Serono SDTM model. Based on NCI published SDTM terminology including the Merck sponsor specific extensions and the appropriate metadata required for maintenance and populating the define.xml (e.g. synonyms, codelist codes)
 - SDTM Model **VLM** (Value Level Metadata), contains...
 - Definition / Listing of the Value Level Metadata (e.g. xxTESTCD's, xxCAT's) specified for the Merck Serono SDTM model. Based on assumptions to collect appropriate metadata required for maintenance and populating the define.xml (e.g. enable nesting of VLM in define.xml)

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Governance Teams

- **General** Data Standards Team (eCRF, paper CRF modules)
- **Therapeutic** Area Data Standards Team (eCRF, paper CRF modules)
 - Oncology
 - (Neurology)
 - (Reproductive Health Care)
- **SDTM** Team (annotated CRF, SDTM data model, CT, VLM)
- **ADaM** Team (ADaM data model, CT, VLM)



Governance Team(s) Responsibilities (I)

- Development and maintenance of **new standards**
- Assessing the impact of **new releases** of CDISC standards and related guidance from Health Authorities on the company specific standards
- **Freezing** standards which are no longer in use
- Providing general rules and conventions for **company specific use** of general data standards, controlled terminology, CDISC SDTM and ADaM



Governance Team(s) Responsibilities (II)

- **Training** on our standards
- Providing expert **guidance** on the application of the standards
- Check **compliance** of Merck Serono standards to existing standards (CDISC, NCI)
- **Exemption** handling



SDTM Governance@Merck: Organisation

- SDTM Governance Team
 - SDTM Librarians plus CT / DST / ADaM Team delegates (plus adhoc members of the SDTM Extended Team)
 - regular TC calls
 - **decisions** on updates of Merck Serono standards (due to CDISC updates, CT updates, FDA requests ...)
 - **discussion** of change requests
 - responsible for creation, use, maintenance and documentation of **SDTM standards**
 - responsible for **training** on SDTM topics (for SDTM Experts, SDTM Independent / Senior Experts, Data Management, Biostats, Regulatory, other departments)

SDTM Governance@Merck: Roles

▪ Roles for the Governance Process

– SDTM **Expert**

- 1st level support for SDTM related topics within GCDS (Mapping and EF process)
- no independent decision making

– SDTM **Independent / Senior Expert**

- (1st and) 2nd level support for GCDS and SDTM expertise (min. 2 years SDTM Expert experience or comparable)
- support for Librarian: 1st review of EF, if applicable promotion of EF to Librarians Team

– SDTM **Librarian**

- decision maker for Exemption Forms
- creation, maintenance and documentation of SDTM standards
- representation of Merck Serono interests in CDISC world
- mentorship for SDTM (Independent) Experts

– **Controlled Terminology Librarian**

- maintenance of Controlled Terminology (SDTM and ADaM)



SDTM Roles

SDTM Librarian

(5, DAR, RCK)

SDTM Independent / Senior Expert

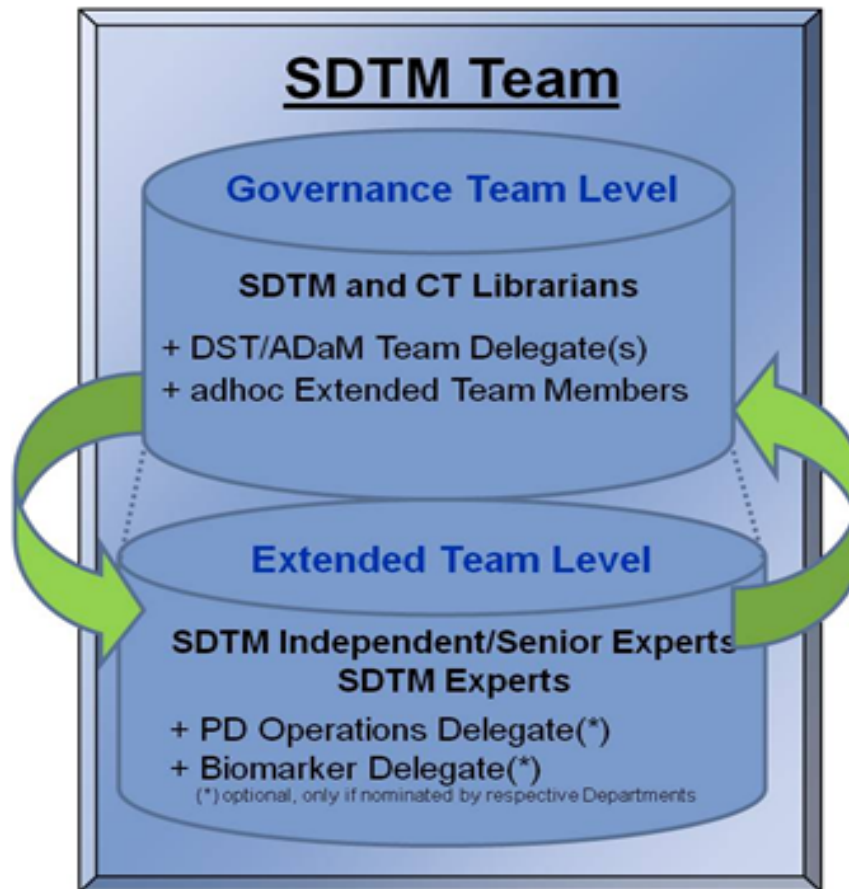
(4, DAR, BEI, TOK)

SDTM Expert

(7, DAR, RCK, BEI)

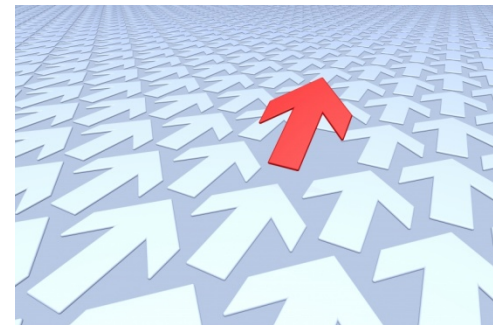


SDTM Governance



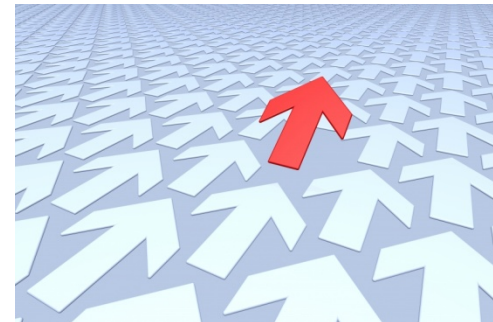
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- People / Roles / Responsibilities
- **Process Flow**
- General Remarks / Challenges / Conclusion

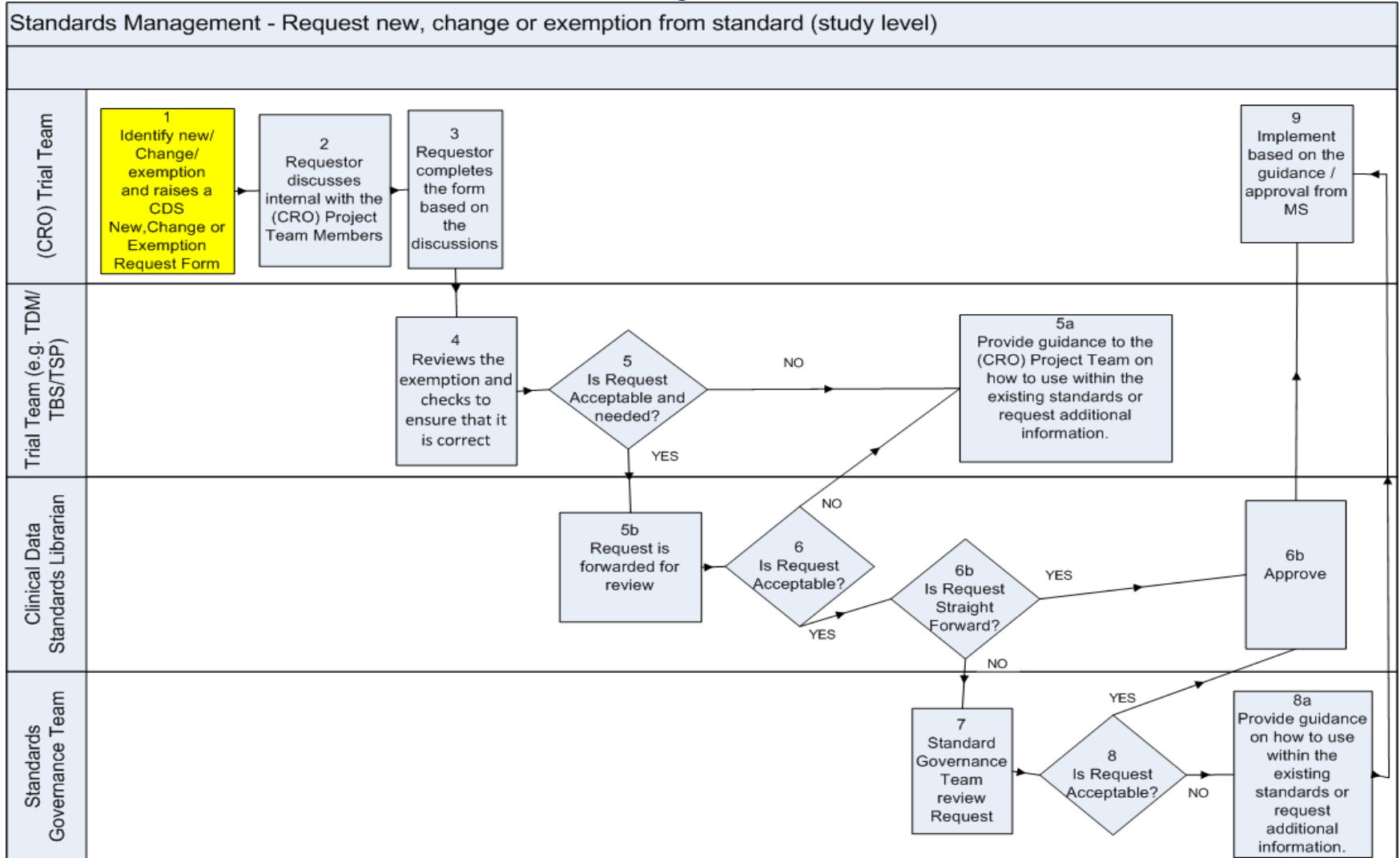


When is the Governance Process used?

- Current clinical data standards do **not cover all the requirements** for setting up any of the trial specifications (e.g. eCRF module, SDTM annotated CRF or data sets, ADaM data sets, Controlled Terminology)
- Anything which does **not comply** with an existing standard
- A “New, Change or Exemption Request Form” (EF) is completed and approved **prior to implementation**
- **Teams involved:** General Data Standards Team, Therapeutic Area Data Standards Team, SDTM Team, ADaM Team



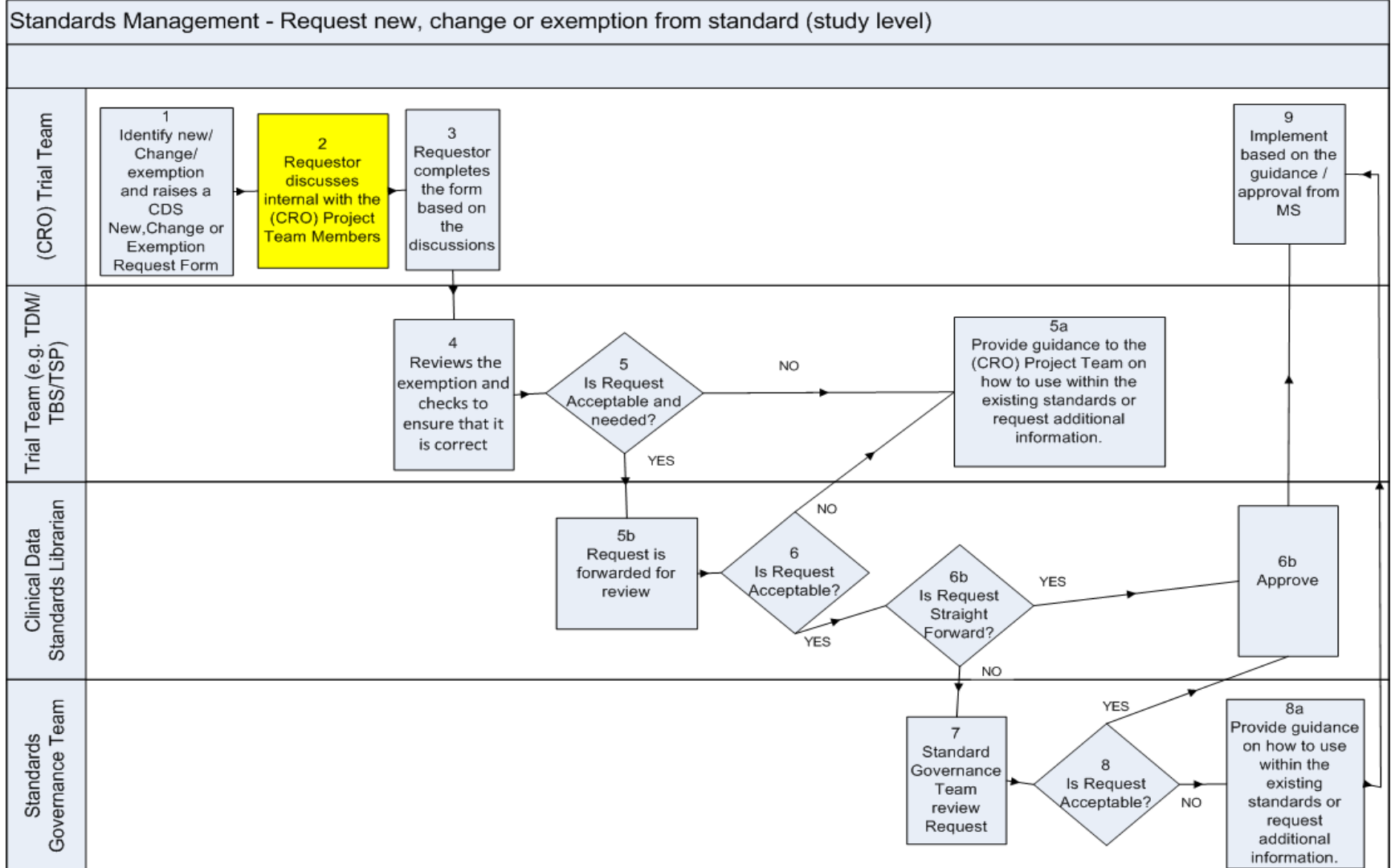
Governance at a Study Level



Governance at a Study Level – Step 1

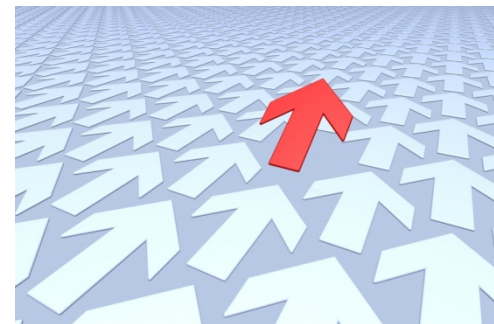
Clinical Data Standards New and/or Exemption Request Form			
General/TA Data Standards/SDTM/ADaM/Controlled Terminology Version:			
Name of Requestor	Trial Phase	Domain Name and Code	
Trial Number	Project Name		Therapeutic Area
Number of general data collection standards used in study:			
Number of therapeutic area data collection standards used in study:			
New forms/modules and domains, please list on the New Form or Domain tab. For SDTM exemptions and/or additions to the most current model, please complete domain name, controlled terminology or VLM as appropriate. For ADaM exemptions, please complete the ADaM domains sheet			
Proposed exemption to the standard:			
Requestor confirms request has been discussed with trial and program team members			
If SDTM related, please state SDTM Independent Expert:			
Rational for the request:			

Governance at a Study Level



Governance at a Study Level – Step 2

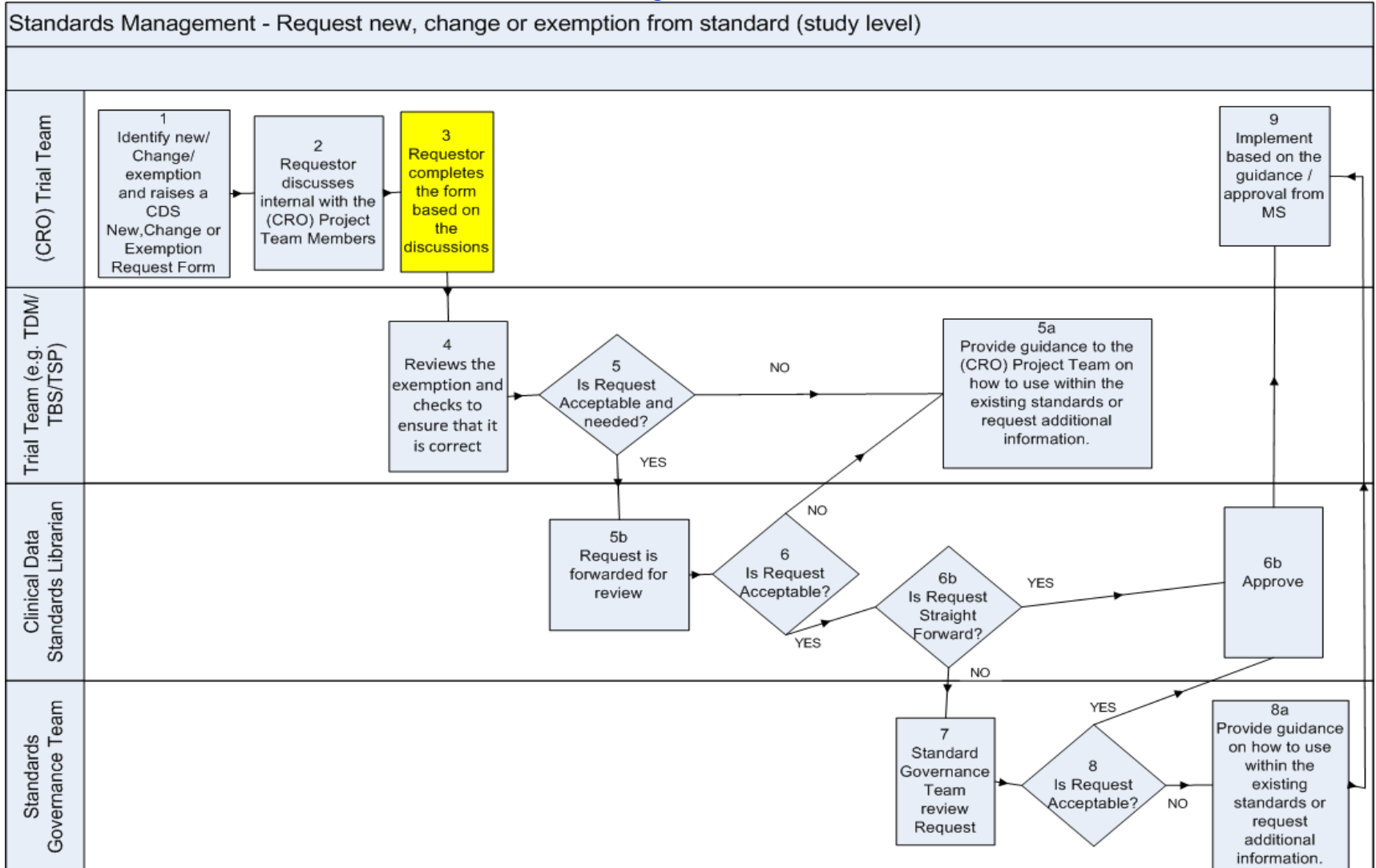
- The (CRO) Project Team Requestor discusses the exemption with the other (CRO) Project Team members to ensure it is needed
- For changes in data standards, CT and SDTM standards, the core reviewers are:
 - Program Data Manager, Project Biostatistician/Project Statistical Programmer and the SDTM specialists
- For changes in ADaM standards, the core reviewers are
 - Project Biostatistician, Project Programmer and if applicable, the ADaM Team Lead



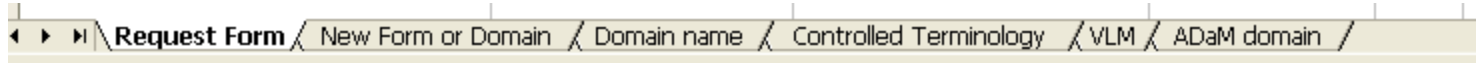
Governance at a Study Level – Step 2

Proposal approved for submission to the relevant Standard Governance Team			
Clinical Data Standards Librarian			
Assessment by the Standards Governance Team			
Request Reference Number (to be completed by the Standards Governance Team):			
DST/TA - approved/rejected/ not needed/not applicable	SDTM - approved/rejected/ not needed/not applicable/partial	ADaM - approved/rejected/ not needed/not applicable/partial	GBS/OS - approved/rejected/ not needed/not applicable
If there is a restriction on the approval please describe the restriction			
If rejected, provide the rationale for the response and/or an alternative proposal:			

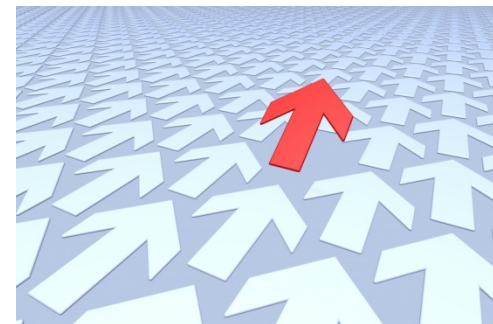
Governance at a Study Level



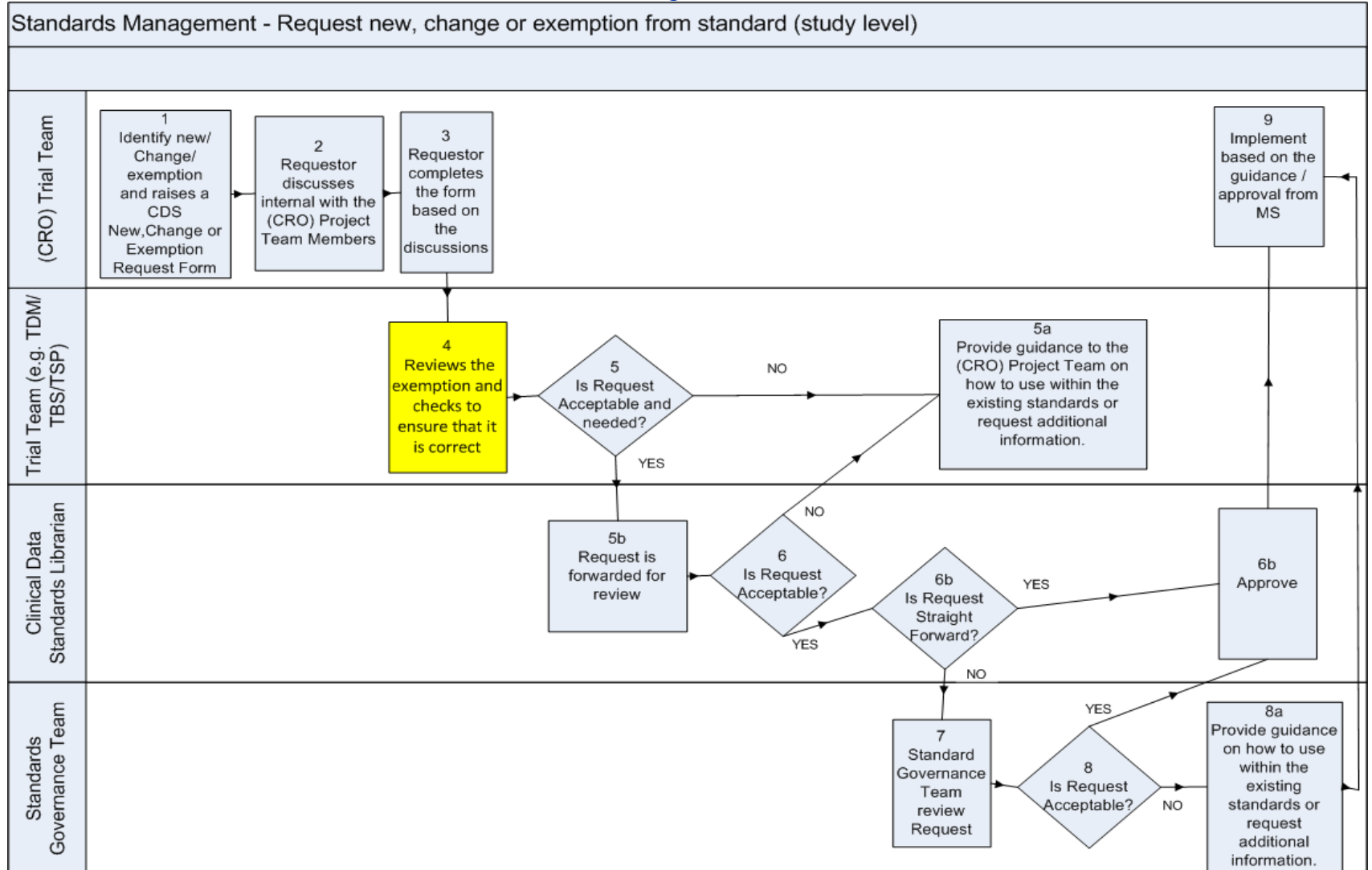
Governance at a Study Level – Step 3



- Where applicable, the Domains, Controlled Terminology and VLM information should be completed
- The completed form is sent to the Trial Team Contact in either GCDS or GBS depending on the type of request



Governance at a Study Level



Clinical Data Standards New, Change or Exemption – SDTM Domain Name Sheet

DOMAIN	OBSCCLASS	VARNAM	VARLABEL	DEFTYPE	CT	VLM	COM_E	Approval?	
YB	Interventions	STUDYID	Study Identifier	Char				yes	
YB	Interventions	DOMAIN	Domain Abbreviation	Char				yes	
YB	Interventions	USUBJID	Unique Subject Identifier	Char				yes	
YB	Interventions	YBSEQ	Sequence Number	Num				yes	
YB	Interventions	YBTRT	<i>Interventions Name</i> Name of Intervention	Char				yes	for approval: please change the original (red) wording to the black one,
YB	Interventions	VISITNUM	Visit Number	Num				yes	
YB	Interventions	VISIT	Visit Name	Char				yes	
YB	Interventions	ETCD	Element Code	Char				yes	
YB	Interventions	ELEMENT	Description of Element	Char				yes	
YB	Interventions	EPOCH	Epoch	Char				yes	
YB	Interventions	YBDTC	Date/Time of Tumor Biopsy	Char				yes	
YB	Interventions	YBMETHOD	Method of Tumor Biopsy	Char		*		yes	
YB	Interventions	YBLOC	Location of Tumor Biopsy	Char				yes	
MH	Events	MHLOC	<i>Location</i> Location of Medical History Event	Char				yes	for approval: please change the original (red) wording to the black one,

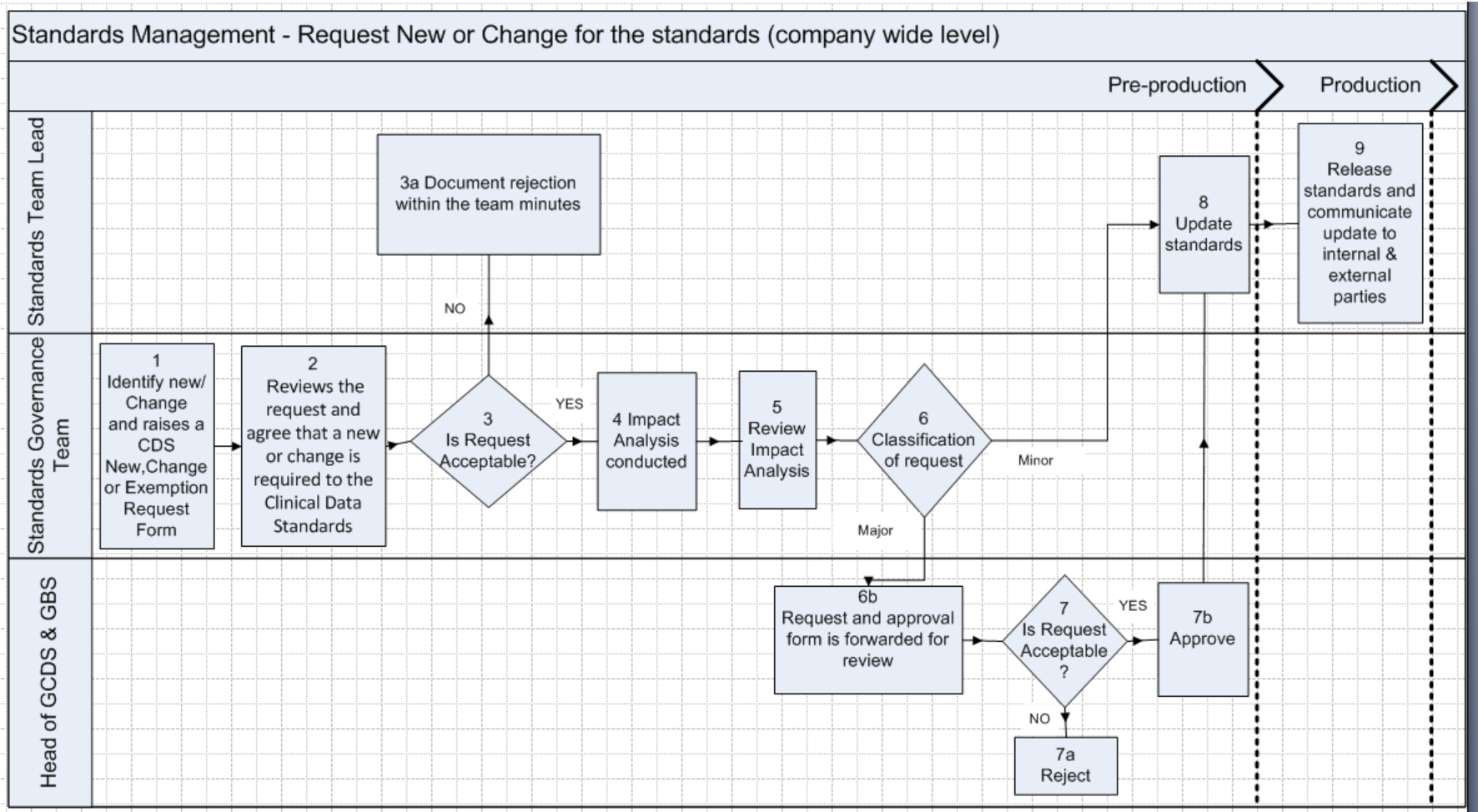
Clinical Data Standards New, Change or Exemption – CT Sheet

CT	CTLABEL	VCODE	VDECODE	Comment/Rationale	Approval?	
CMCAT	Category for Medication	PRIOR ANTI-CANCER TREATMENT	Prior Anti-Cancer Treatment	Study specific new category	yes	
LBCAT	Category for Lab Test	MOLECULAR MARKERS	Molecular Markers	Disease specific laboratory test	yes	
TRCAT	Category for Tumor Results	IRRC	irrc	Study specific	no	TRCAT is not a variable for TR domain in our data model. Please use a supplemental variable to keep this information
XXSCAT	Subcategory for Study Maintenance	IMMUNOMONITORING	IMMUNOMONITORING Immunomonitoring	Study specific	yes	for aproval: but please use mixed case for VDECODE (use the wording in black colour)

Clinical Data Standards New, Change or Exemption – VLM Sheet

DOMAIN	VLMNAM	VCODE	VDECODE	Comment/Rationale	Approval?	
LB	LBTESTCD	AKT1	Serine/threonine-protein	Study specific	yes	
LB	LBTESTCD	ALKTR	ALK Translocation	Study specific	yes	
LB	LBTESTCD	ANCA	Anti-Neutrophil Cytoplasmic Antibody	Study specific	yes	
LB	LBTESTCD	DDR2	DDR2 Discoidin Domain Receptor Tyr Kinase 2	Study specific	yes	for approval: please change the original (red) wording to the black one.
LB	LBTESTCD	ELEC	Serum electrophoresis	Study specific	yes	
SUPPDS	QNAM	RADASS	Radiologic Assessment	Variable not in Standards. Added for exemption.	yes	
SUPPDS	QNAM	SUFFLUP	Agreement to be Followed for Survival	Variable not in Standards. Added for exemption.	yes	
SUPPEG	QNAM	EGABN EGABNSP	ECG Abnormality	Variable not in Standards. Added for exemption.	yes	for approval: please change the original (red) wording to the black one.
SUPPEX	QNAM	MODDTC	Administration Modification Start Date/Time	Variable not in MS Standards. Added for exemption.	yes	
SUPPEX	QNAM	MODIFD	Administration Modification Details	Variable not in MS Standards. Added for exemption.	yes	

Governance for Changes to the Standards



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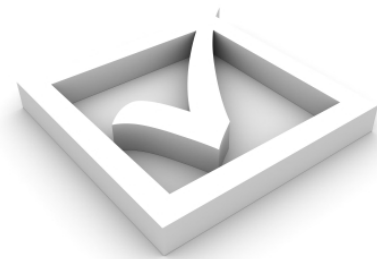


General Remarks

- We keep all approved versions of our Merck Serono standards
- Project Team needs to decide
 - **which version** of Merck Serono standard shall be used
 - whether / **when to move** to a newer version
- SDTM Governance Team decides
 - when to release new **Merck Serono standards**
 - how / when to implement new **CDISC updates**
 - when to implement a new version of **NCI CT** (updated 3-4 times / year)

General Remarks

- KPIs (Key Performance Indicators)
 - **number of standardised CRF modules** used in a trial
 - “Average compliant rate in % on the mandatory general data standards for phase I-III studies”
 - “Average compliant rate in % on the mandatory oncology data standards for phase I-III studies”
 - **feedback time** for EF requests



Challenges

- Exemption forms
 - a lot of **work to create**
 - Program Data Manager needs to know which exemptions are already approved for the project, harmonisation within projects important
 - a lot of **work to approve**
 - decision on approval needs knowledge of the project, harmonisation within projects important (currently: manual comparison) – SDTM librarians assigned to certain projects
 - approval of exemptions is based on the version of Merck Serono standards used for the trial
 - **evaluate impact** on general standards



Challenges

- Updates of Merck Serono SDTM standards
 - **case by case decision** whether to include the approved trial specific exemptions into the global SDTM standard
 - Merck Serono SDTM team keeps the **global SDTM standard**, no resources to keep project specific
 - updates of **CT and VLM** close to the updates released by the NCI
 - updates of **SDTM data model** depend on resources within the SDTM team, the number and importance of new releases by CDISC
 - **project specific CT / VLM** are not yet kept in the SDTM data model, needs to be improved in the future



Conclusion

- Merck Serono way of maintaining standards by using EF
 - **manually** processed
 - **time-consuming**
 - a lot of **experience** and know-how necessary
 - good **indicator** where our standards need to be updated/expanded
- More **frequent updates** of standards necessary to reduce amount of work for EF handling
- **Future:** Clinical Data Repository
 - General standards available in **standard library**
 - EF request and approval process **embedded** in system
 - **project specific** standards will be kept in the system

