March 9 2021

Submission and assessment of a new clinical trial application when the Regulation (EU) No 536/2014 applies

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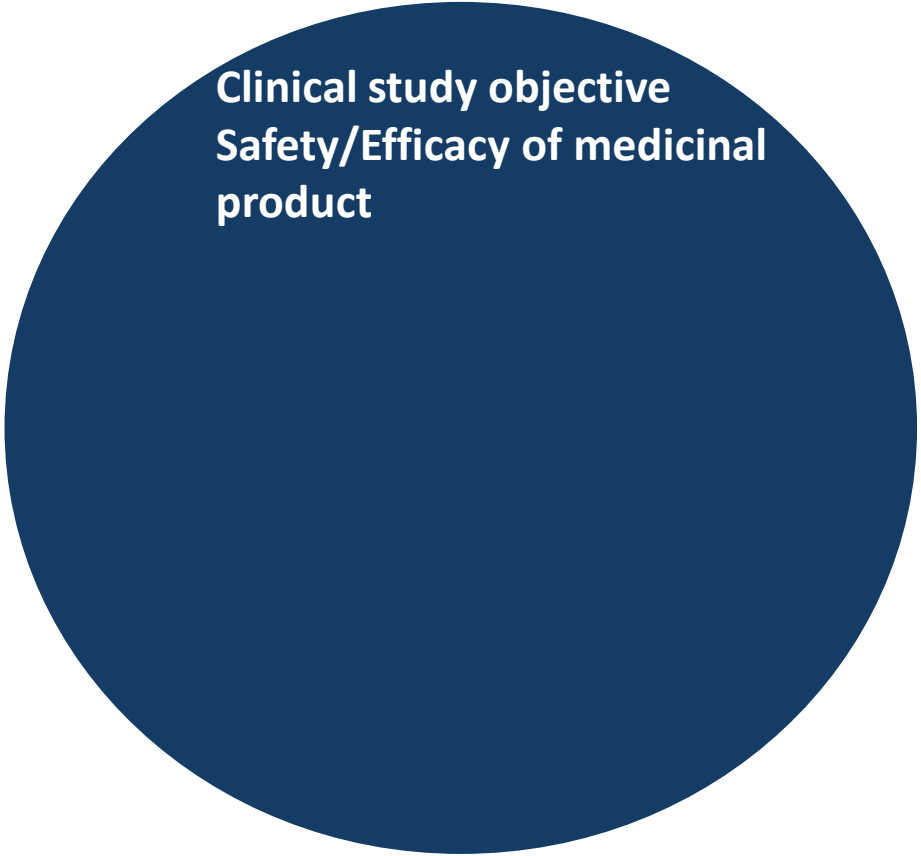
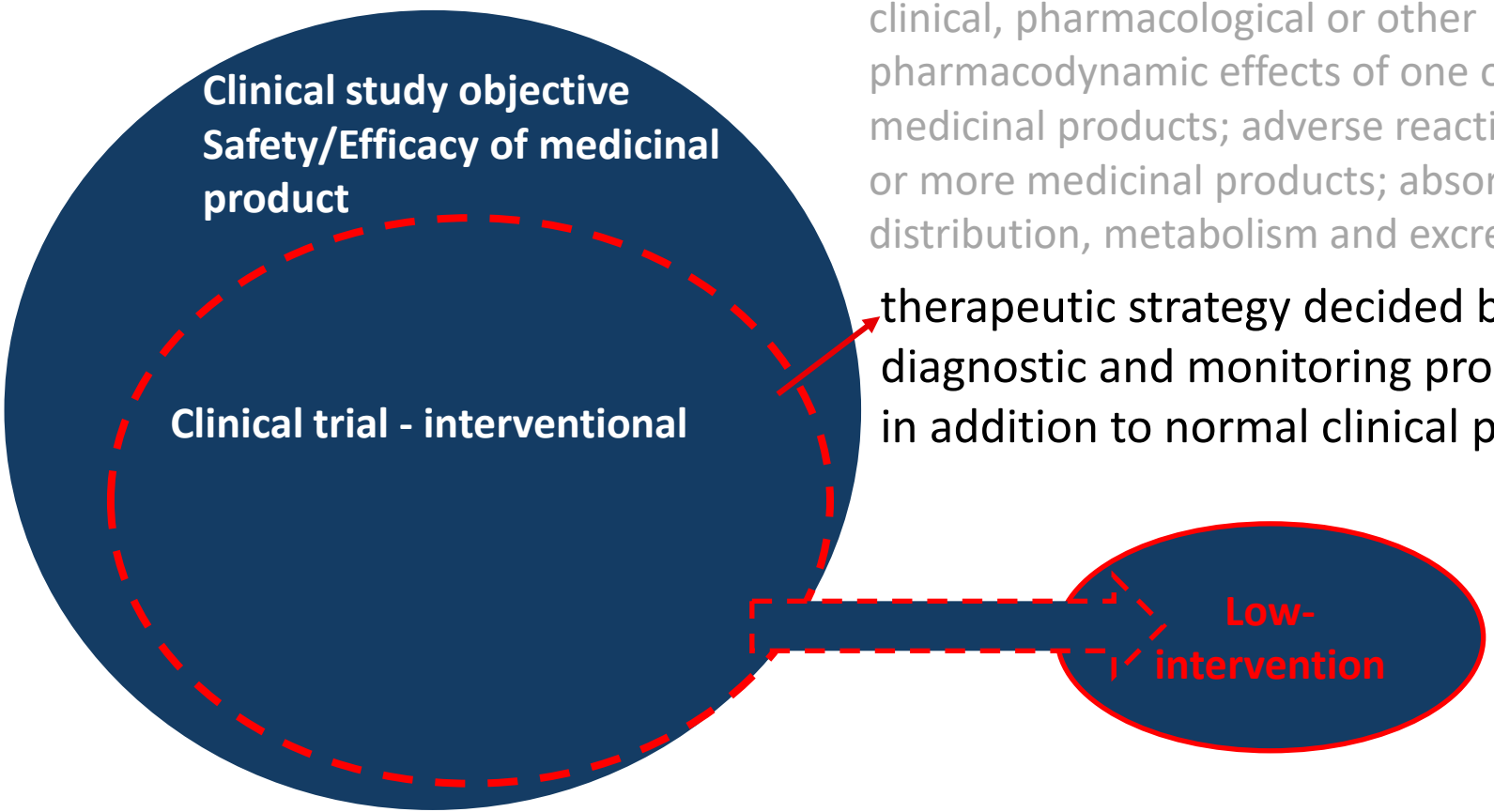
EC-DG SANTE/HMA-CTFG/EMA joint training on Regulation (EU) No 536/2014

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY



clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; adverse reactions to one or more medicinal products; absorption, distribution, metabolism and excretion



clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; adverse reactions to one or more medicinal products; absorption, distribution, metabolism and excretion

therapeutic strategy decided by protocol, diagnostic and monitoring procedures in addition to normal clinical practise

Validation

Portal

Sponsor submits initial application dossier

Assessment Part I

Initial clinical trial application

Assessment Part II

Notification

Sponsor receives notification/ decision

Portal

Sponsor definition

- an individual, company, institution or organisation responsible for initiation, management and setting up financing of a clinical trial

Sponsor submits an application to the Portal

- Submits application to the intended Member States concerned (MSCs)
- Proposes one of the Member States concerned as reporting Member State

- Language requirement for application - decision by each Member State.

"…consider accepting, for documentation not addressed to the subject, a commonly understood language in the medical field…"

Application dossier Part I and Part II

- **Unique EU trial number**

- **Cover letter** - list all investigational medicinal products (IMPs) and Auxiliary Medicinal Products (AxMPs) and their regulatory status, if low-intervention trial, vulnerable populations, first-in-human, scientific advice, paediatric investigation plan, special IMP (narcotic, psychotropic, radiopharmaceutical), genetically modified organism (GMO), informed consent simplified means (randomisation of subject groups - not individuals in cluster trial), location of Reference Safety Information
- If resubmission - describe changes

Application dossier Part I

- **Protocol** with synopsis
- **Investigator's brochure**
- **Manufacturing and import** (products authorised outside EU)
- Investigational Medicinal Product Dossier
  - **IMPD - Quality**
  - **IMPD - Safety and Efficacy**
- Auxiliary Medicinal Product (**AxMP**) - required in the clinical trial but not IMPs
- **Scientific advice**, Paediatric Investigation Plan (**PIP**)
- **Labelling**

Application dossier Part II

- Recruitment arrangements
- Informed consent and subject information
- Subject compensation
- Suitability of investigator and trial facilities
- Proof of insurance/damage compensation
- Proof of payment
- Data protection
- Biological samples

Application - protocol 1

PROTOCOL

- Objective, design, methodology, statistical considerations, purpose and organisation of the clinical trial (if patients involved in design?)
- Synopsis (understandable to a layperson, maximum two pages, recommendations to sponsors what to include)
- Trial conduct in accordance with protocol, Principles of GCP and Regulation
- If emergency situation trial: scientific ground for clinically relevant benefit for individual subject
- Investigational and auxiliary medicinal product description (IMP, AxMP) if authorised: used within marketing authorisation terms, exposure, justification of dosing etc.

Application - protocol 2

PROTOCOL

- Tracing, storing, destroying and returning the investigational medicinal product, accountability procedures and how blinding secured
- Efficacy and safety parameters, timing for assessing, recording, and analysing
- Trial end points - primary and secondary
- Description of trial population (inclusion, exclusion, relevance including gender selection - when relevant: lifestyle considerations, permitted and prohibited concomitant medication)
- Withdrawal criteria (from treatment or entire trial?)

Application - protocol 3

PROTOCOL

- Ethical considerations, including recruitment and informed consent procedure, use of biological samples, data protection etc. (i.e. overview of issues included in more detail in the Part II dossier)
- Known, potential and anticipated benefits/risk - IMP/AxMP, Interventions, Disease
- Expected duration of subject participation
- Discontinuation (parts or entire trial)
- If applicable: arrangements for taking care of subjects after participation in clinical trial ended
- Maintenance of randomisation code - emergency unblinding

Application - protocol 4

PROTOCOL

- Data recorded directly on case report form - source data
- Subject compliance
- Monitoring
- Statement from sponsor confirming investigators and institutions involved in trial allow monitoring, audits and regulatory inspections, including access to source data and documents
- Publication policy
- End of /Start of trial - definitions
- Reasons for submission of summary of results after more than one year (paediatric trial 6 months)

PROTOCOL

Application - protocol 5 - safety

- Details on recording adverse events by investigator, reporting of relevant adverse events by the investigator to sponsor; reporting of suspected unexpected serious adverse reactions by sponsor to Eudravigilance; after adverse reactions - type and duration of follow-up
- Special adverse events or laboratory anomalies critical to safety that must be reported by investigator to sponsor, and if any serious adverse events are considered exempted from immediate reporting by investigator to sponsor
- Rational if single safety report on all investigational medicinal products used in the clinical trial
- Charter of the Data Safety Monitoring Committee

Application - protocol 6 - statistics

PROTOCOL

- How minimise bias (randomisation, blinding)
- Statistical methods and level of significance
- Interim analyses - timing, rational
- Sample size and rational for choice (power calculation)
- Procedures for missing, unused, and spurious data and for reporting any deviation from the original statistical plan
- Selection of subjects to be included in the analyses

Application - protocol - comparison ICH draft template

ICH protocol template under development - input provided by Clinical Trials Facilitation and Coordination Group (CTFG) and Clinical Trials Expert Group (CTEG) - need to comply with regulation

- ICH harmonisation for better health

Final Concept Paper

ICH M11: Clinical electronic Structured Harmonised Protocol (CeSHarP)
dated 14 November 2018

Endorsed by the Management Committee on 15 November 2018

Investigator's Brochure

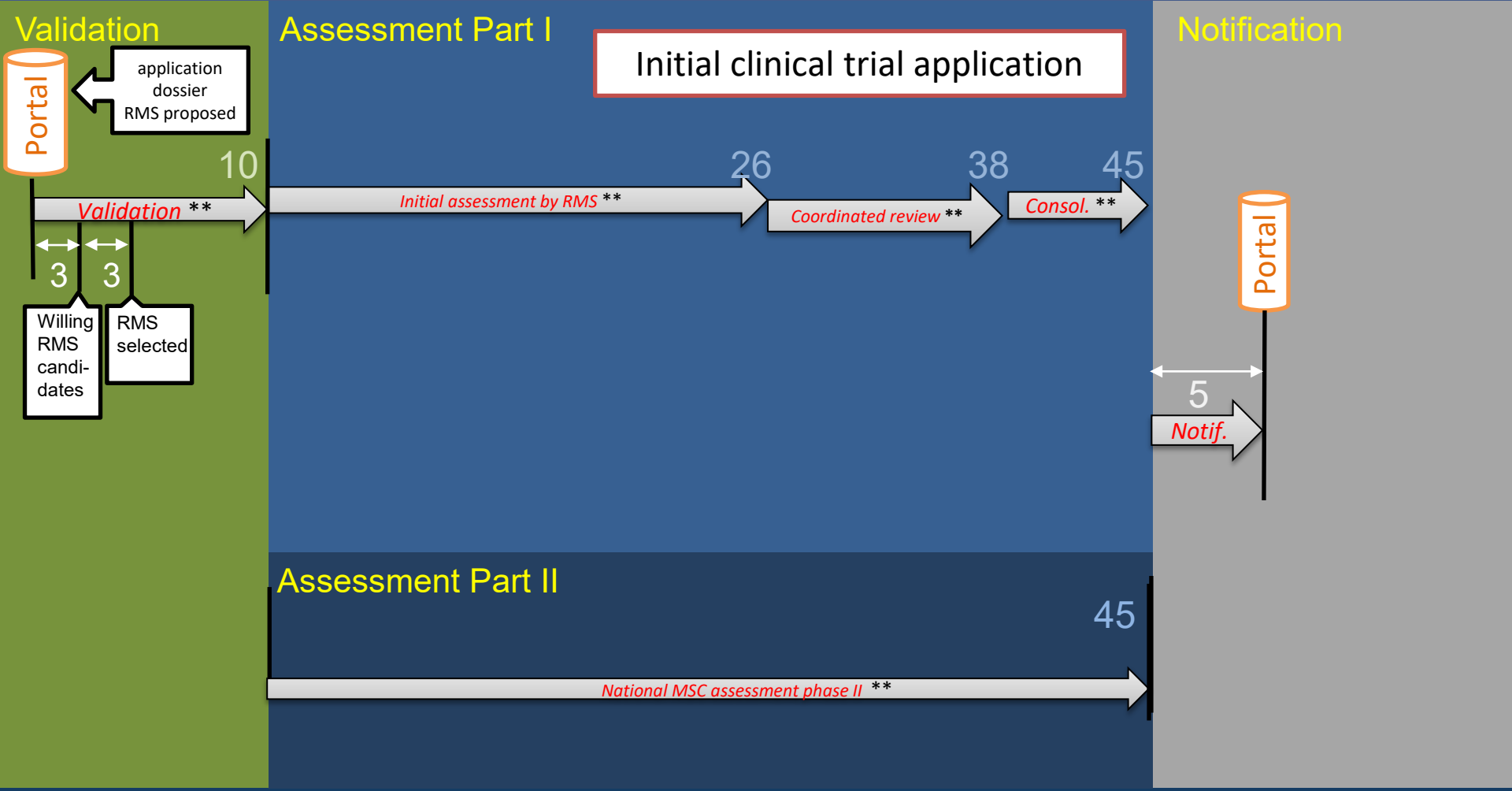
IB

- Basis = allow investigator to make unbiased risk-benefit assessment of trial
- All available information and evidence supporting rationale for trial and safe use of IMPs (AxMPs)
- SmPC - if authorised IMP
- Reference Safety Information (RSI) on serious expected adverse reactions, describing frequency and nature

IMPD & other docs

GMP compliance documents, IMPD Quality, IMPD safety and efficay etc.

- IMPD - two documents - separate on quality (never public according to confidentiality rules)
- Quality Module 3 of ICH Common Technical Document format
- IMPD-safety and efficacy with non-clinical pharmacology, toxicology data and statement of good laboratory practice status as well as data from previous clinical trials and human use
- Auxiliary Medicinal Product Dossier
- Scientific advice, Paediatric investigation plan (PIP)
- Labelling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Willing RMS candi-dates
RMS selected
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National MSC assessment phase II **

RMS selection for multinational trials Part I

- First 3 days all MSCs express willingness
  - Only one willing = selected RMS (no further discussion next 3 days)
- Next 3 days all MSC should agree on RMS selection
  - Several willing = discussion
  - List of candidates in order of optimal workshare algorithm (number of RMS-ships in an MSC as a percentage of all multinational clinical trial applications submitted to that MSC during the last 12 months)
  - If no agreement on selection, the RMS will be the one proposed by the sponsor

RMS selection for multinational trials Part I

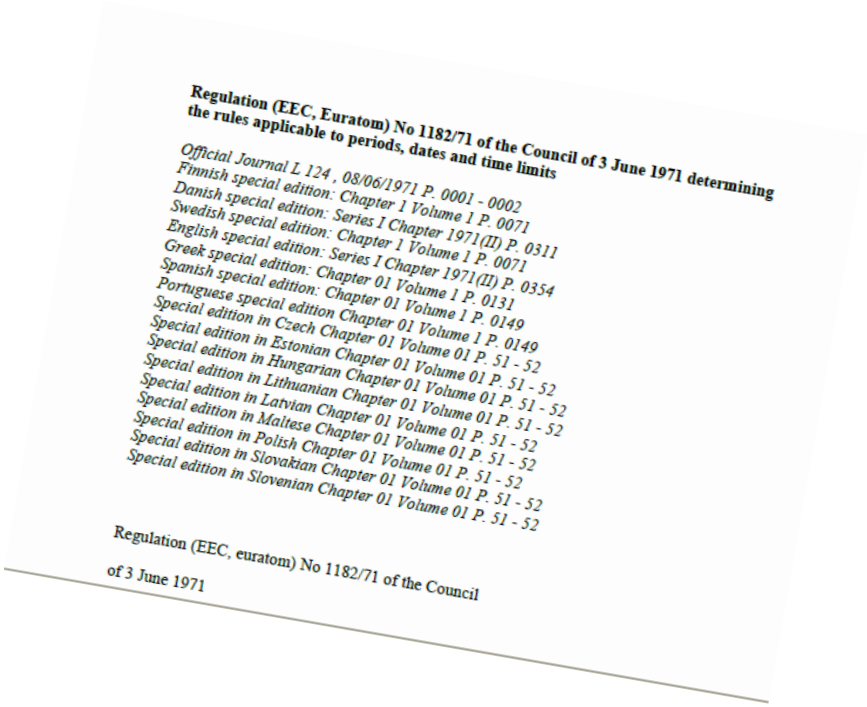
- If no MSC willing Day 3
  - Discussion, possibility to reexpress willingness for all MSCs
  - If still none willing or disagreement - the MSC proposed by the sponsor will be RMS

- RMS responsible for coordination of all Part I procedures throughout the life cycle of the clinical trial - irrespective if trial continues in MS or not

All timelines = calendar days

Application of Regulation (EEC, Euratom) No 1182/71

- Due date must never fall on weekend or official holiday
- No time period shorter than two consecutive working days

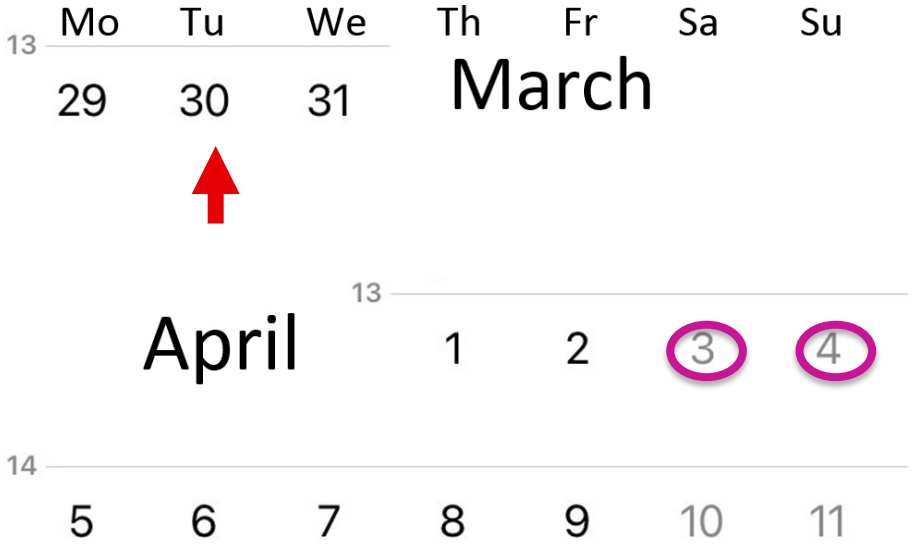


Example how to count calendar days taking regulation

Weekend

Due date cannot fall on weekend = instead moved to next day

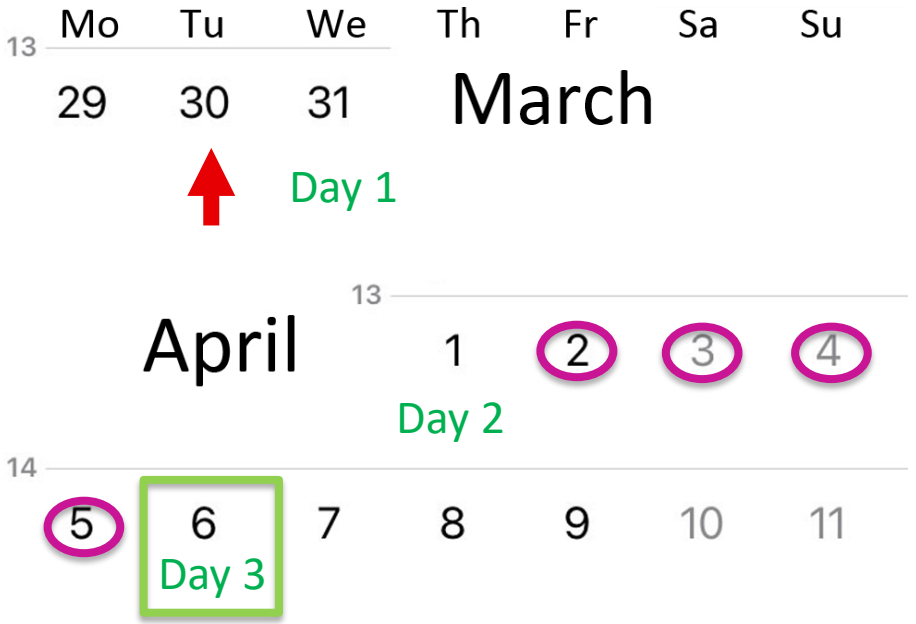
Start counting days the day after application submission (red arrow)



Multinational initial application, two MSCs

Weekend or official holiday (for green MSC April 2,5 and weekend)
Due date (Day 3) moved forward

Green MSC 1 - Day 3 = April 6

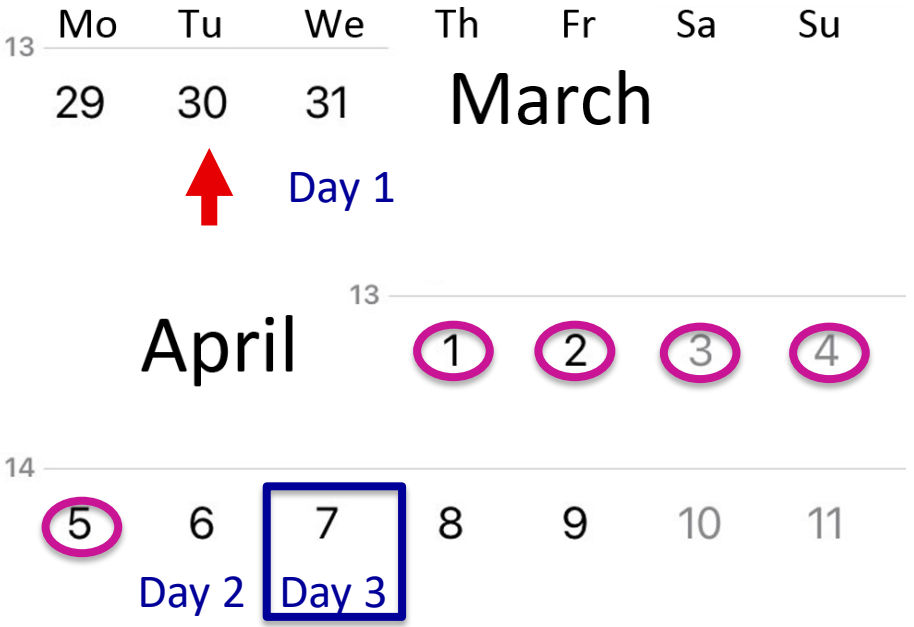


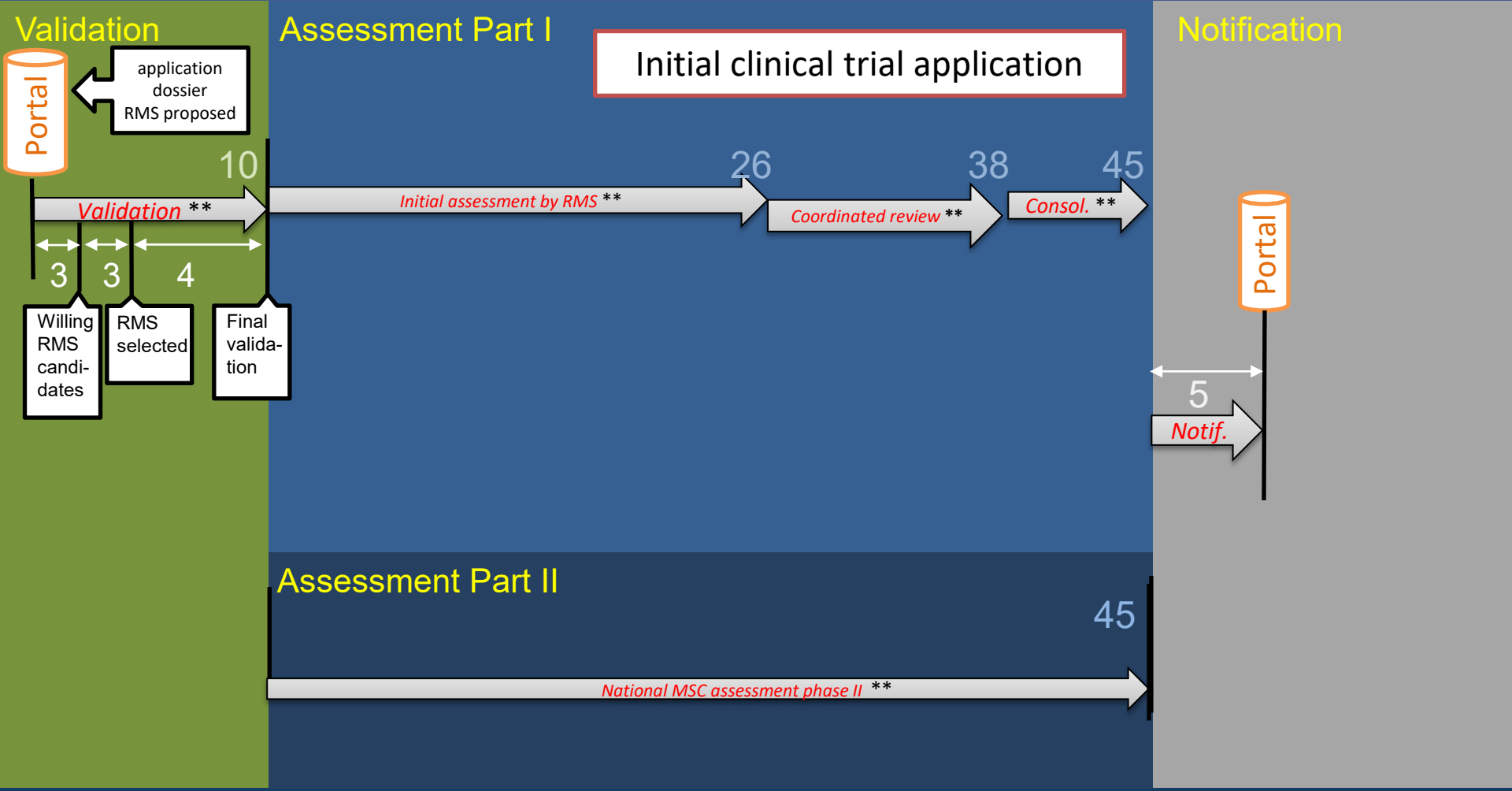
Multinational initial application, two MSCs

Weekend and official holiday (for blue MSC April 1,2,5 and weekend)

Due date (Day 3) moved taking ’slowest calendar’ into consideration

Blue MSC 2 - Day 3 = April 7

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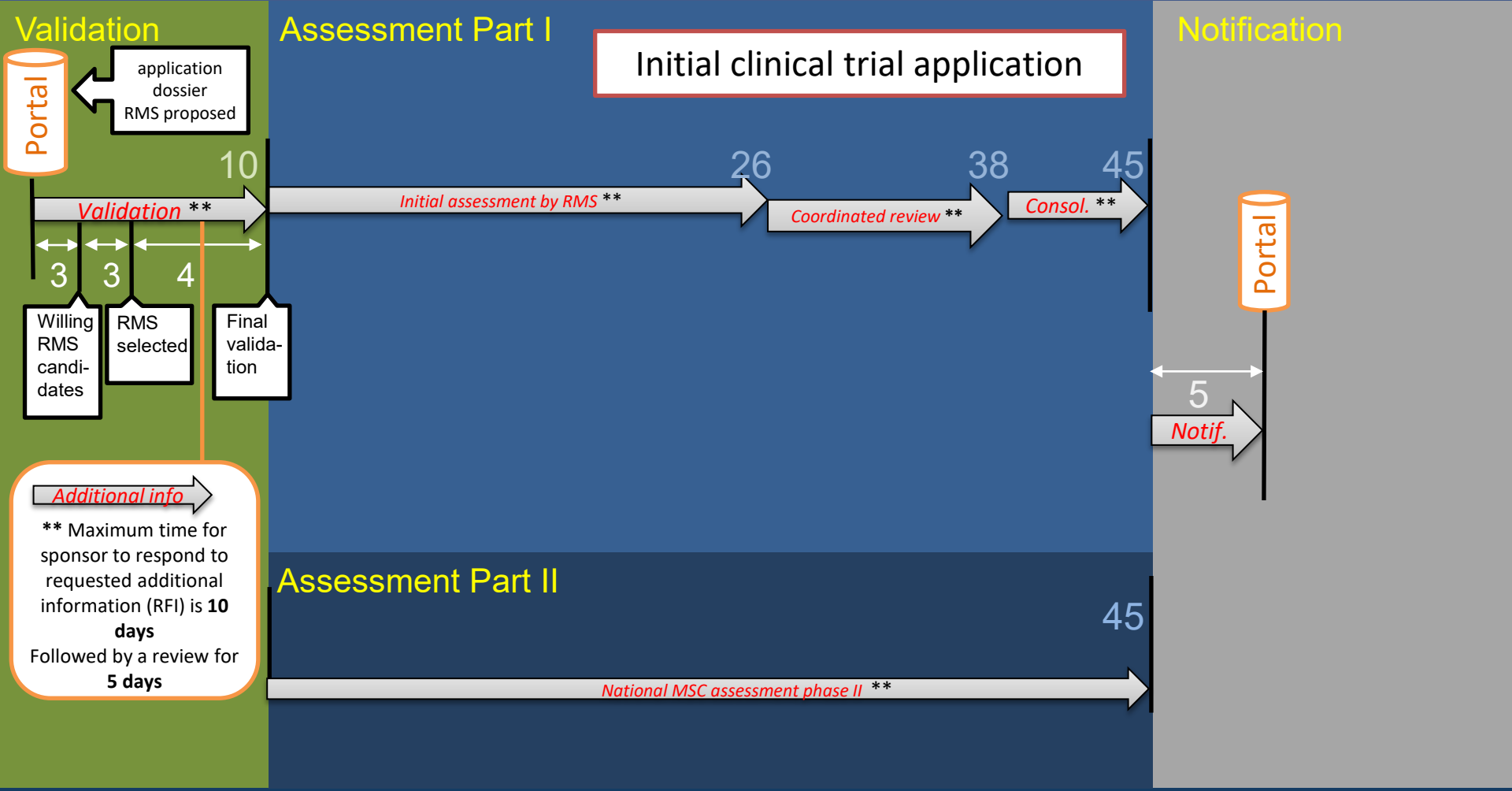
Validation

- Does clinical trial fall within scope of Regulation?
- Is the application dossier complete (Annex I)?
- Day 7 - deadline to provide considerations for MSCs on validation
- RMS sends Request for information (RFI) on validation to sponsor, response within 10 days, final decision within 5 additional days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Additional info
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Followed by a review for 5 days
Assessment Part II
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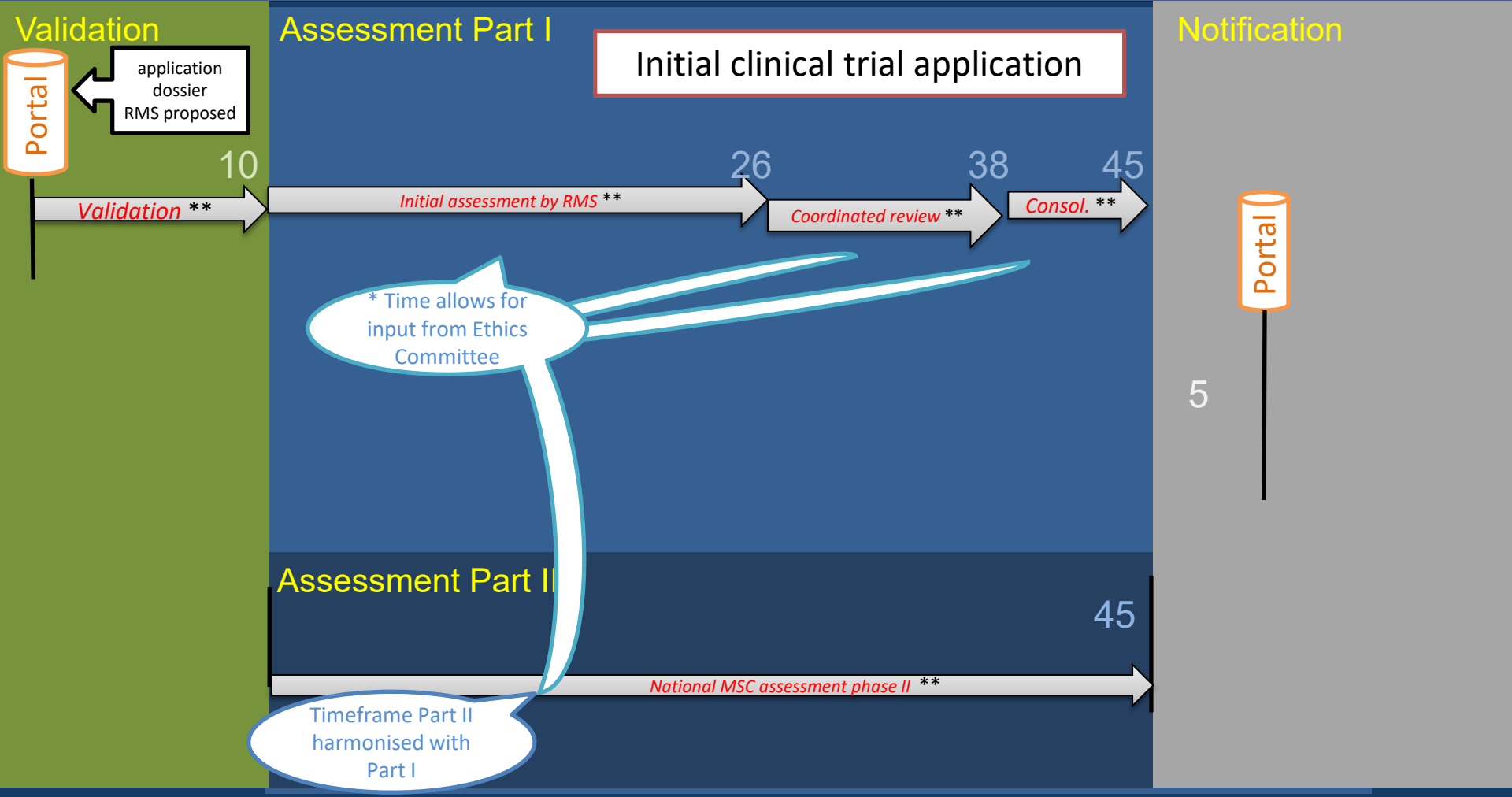
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Timeframe Part II harmonised with Part I

Assessment Part I

Compliance with legal requirements?

In line with current state of scientific knowledge?

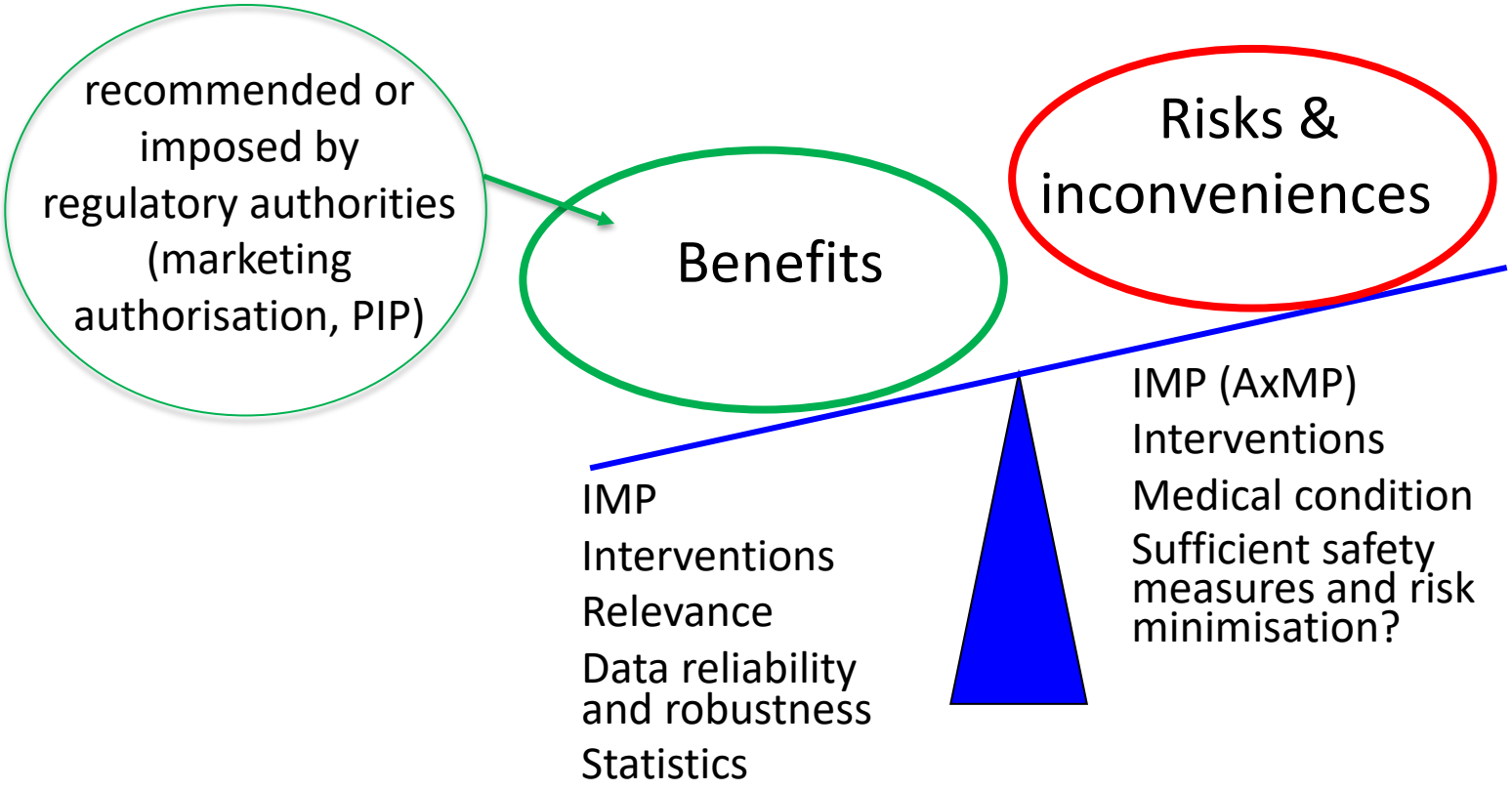
- Low-intervention trial
- Manufacturing and import of investigational medicinal products and auxiliary medicinal products
- Labelling
- Completeness and adequateness of required documents required in the application dossier

Assessment Part I

- Benefit - individual, group or public health?
- Emergency situation - scientific grounds to expect potential of direct **clinically relevant benefit** for the individual subject

  "…a measurable health-related improvement alleviating suffering and/or improving health of the subject, or in the diagnosis of its condition…"
- Risk - only to subject (not environment, e.g. GMO)

Assessment Part I



Assessment

- Impartial assessors - no conflict of interest (e.g. vs. sponsor, investigator, trial site, financing institution), yearly financial declaration
- Necessary qualifications and experience
  - relevant disease and patient population
  - esp. for trials with vulnerable groups (minors - paediatric expertise, incapacitated subjects, subjects in emergency situations)
- At least one layperson in assessment

Assessment Reports - key documents by RMS (Part I), each MS (Part II)

- Required documents as a basis for RFI/decision
- Part I: templates tested in Voluntary Harmonisation Procedure (VHP)
- Templates not further revised before clinical trial regulation applies
- Confidentiality rules apply to draft assessment report

1 ADMINISTRATIVE INFORMATION

EU CT number	2019-500218-42-00
Title of the study	CTCS-5562/ CTCS-7817/ CTCS-8912/ CTCS-9200 Suggestion to download the report templates all at once in Assess_Part_I
Name of sponsor(s) *Note: if there is more than one sponsor the primary contact should be identified*	Panpharma
Trial category *(as per EMA Appendix on disclosure rules: EMA/228383/2015 Endorsed)*	Category 1 ☒ Category 2 ☐ Category 3 ☐
Low intervention trial	Yes ☐ No ☒
First in human ☒ Phase I ☒ II ☐ III ☐ IV ☐	
Vulnerable population(s)	Yes ☐ No ☒ See Section 5.4.7

2 INFORMATION ON THE PROCEDURE

Reporting Member State	Name of RMS and contact details:
Other Member States concerned	Germany
Draft AR ☐ Revised Draft AR ☐ Final AR ☐	Date: Date: Date:

Draft assessment report (DAR) separate sections

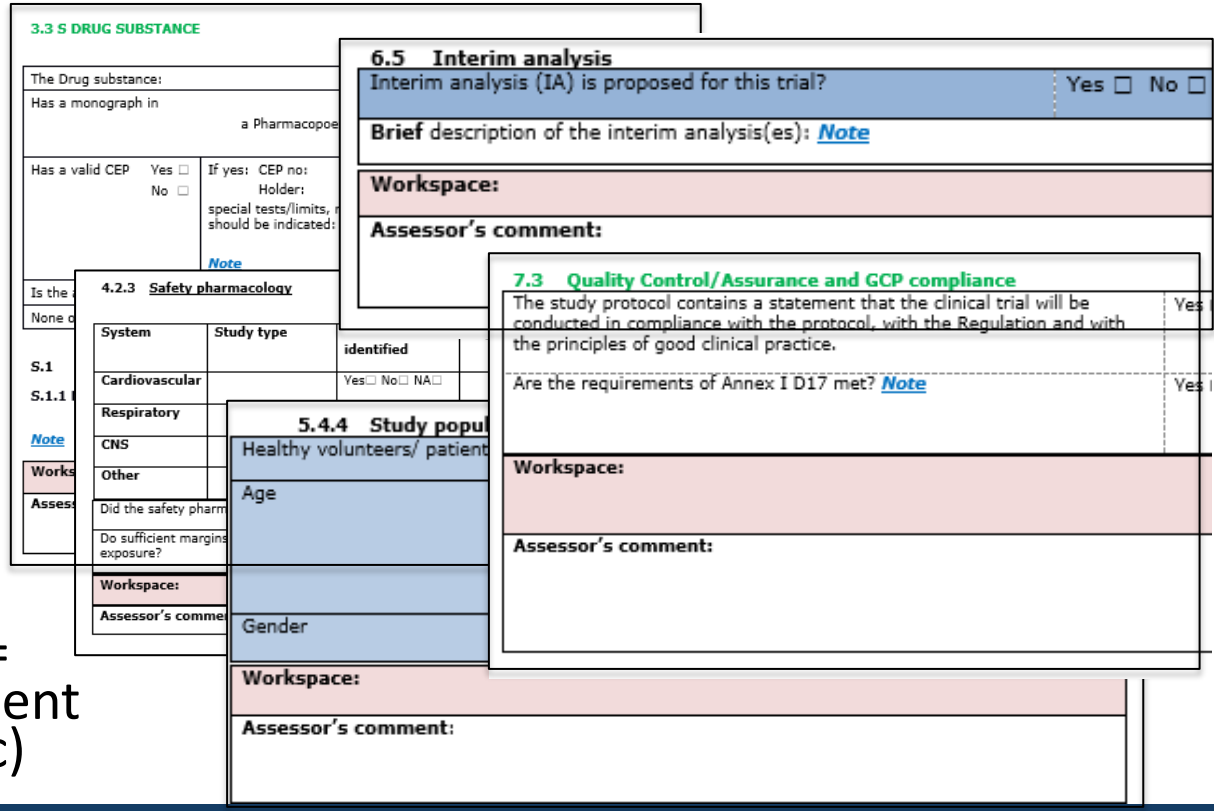
3 Quality
4 Pre-clinical
5 Clinical
6 Statistical
7 Regulatory

Separate ’boxes’:

Aspects assessed

Assessor’s comments

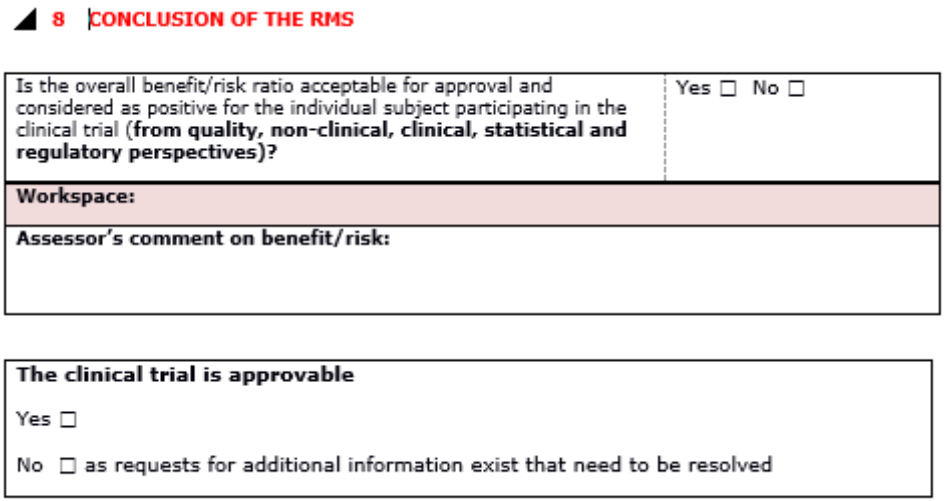
Workspaces (red boxes only for Member States = removed in final assessment report for sponsor/public)



Draft assessment report - conclusion of RMS

- Conclusion
- If ’no’ ticked = RFI to sponsor
- Note:

  MSCs can propose changes to DAR before RFI (communicated as an MSC consideration)



8 CONCLUSION OF THE RMS

Is the overall benefit/risk ratio acceptable for approval and considered as positive for the individual subject participating in the clinical trial (**from quality, non-clinical, clinical, statistical and regulatory perspectives)?**	Yes ☐ No ☐
Workspace:	
Assessor’s comment on benefit/risk:	

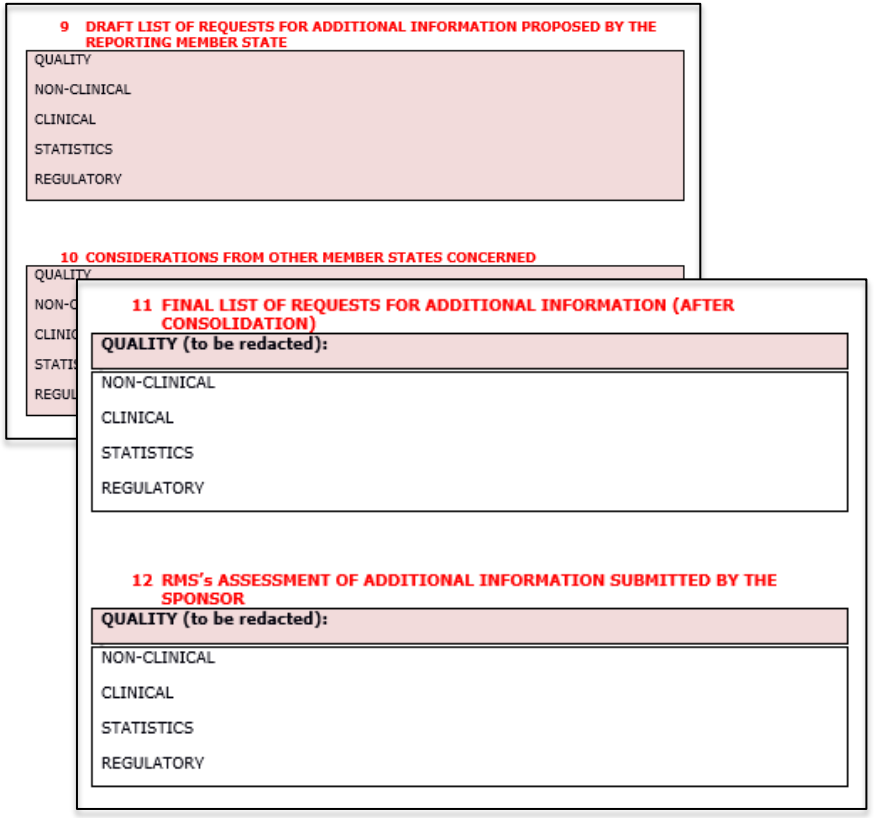
The clinical trial is approvable

Yes ☐

No ☐ as requests for additional information exist that need to be resolved

List of questions (considerations ⟶ RFIs)

- Considerations from RMS/MSCs
- Consolidation by RMS into ’Request for Information’ (RFI) sent to sponsor
- RFI - critical matters that could lead to rejection/condition if not solved (’single question round’)
- RFI - clearly written - clarify if a new version of a document is required
- RMS/MSC assess sponsor’s response and additional information provided

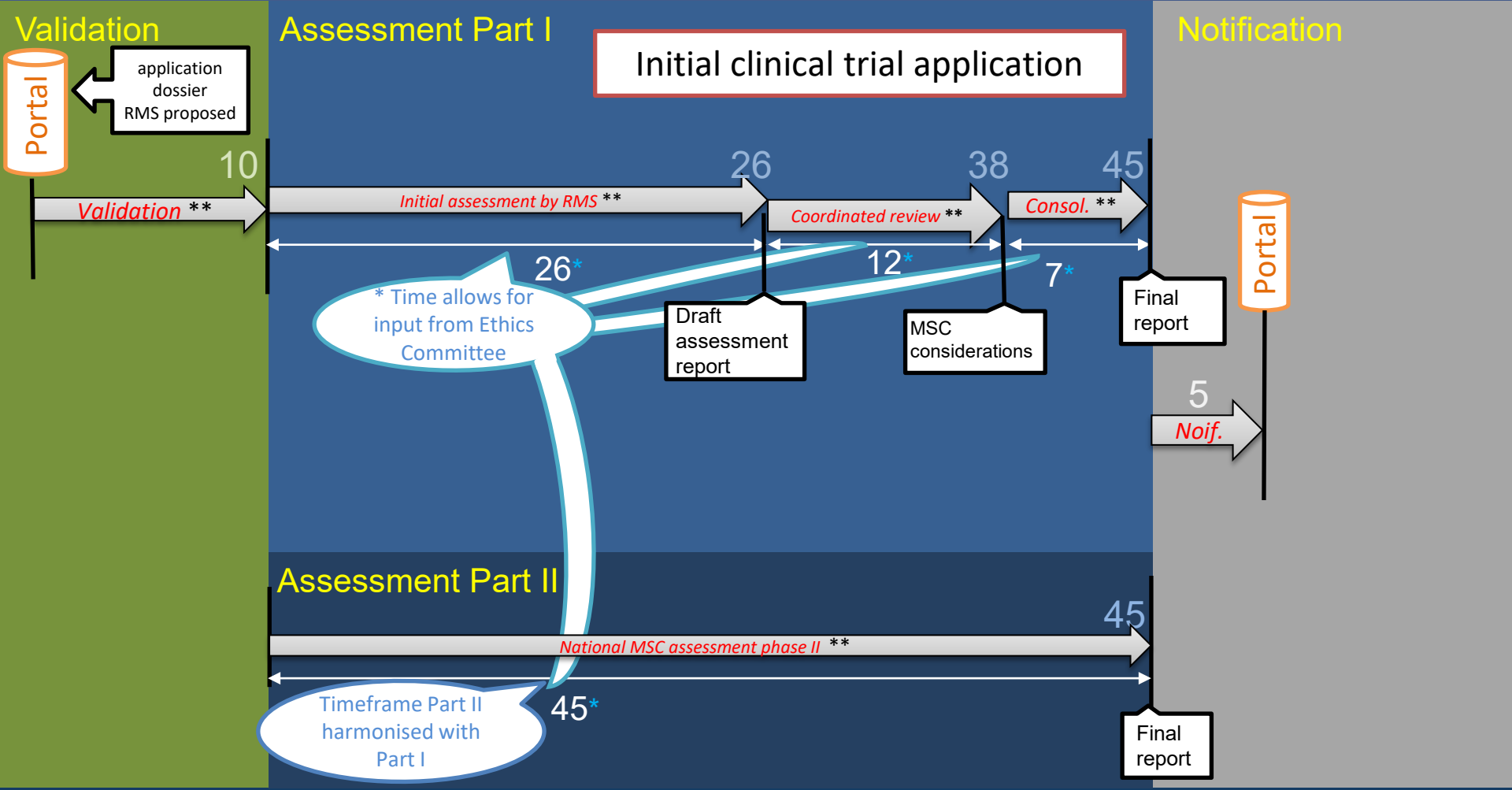


DAR - Final conclusion of RMS

- **Best practice: final DAR circulated to MSCs one day before upload to Portal**
- **Condition - clearly written, based on issue raised as RFI**
- **Clarify if a substantial modification application is required to fulfill condition**

13 FINAL OVERALL CONCLUSION OF THE RMS (as per Art 6(3) of the Regulation)

The Investigator's brochure is complete and adequate	Yes ☐ No ☐
For low-interventional trials only: The clinical trial fulfils the conditions for a low-intervention trial	Yes ☐ No ☐
The conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation	☐
The conduct of the clinical trial is acceptable in view of the requirements set out in the Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion	☐
The conduct of the clinical trial is not acceptable in view of the requirements set out in this Regulation	☐
The wording of conditions or rejection as proposed by the RMS:	
The final agreed wording of conditions or rejects to be sent to sponsor:	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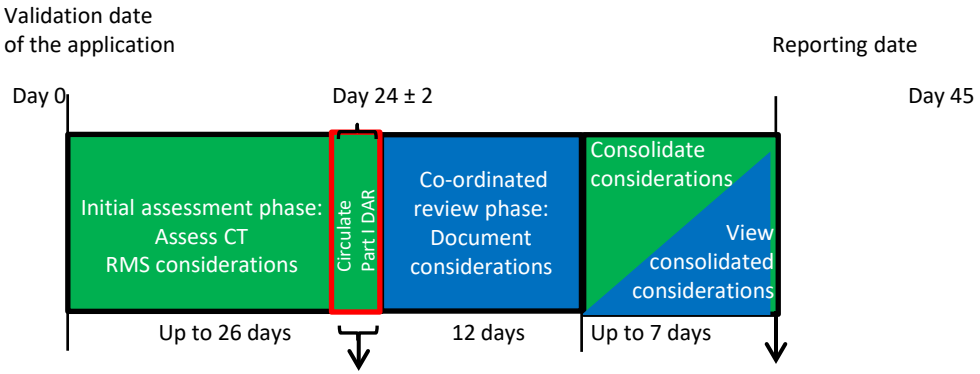
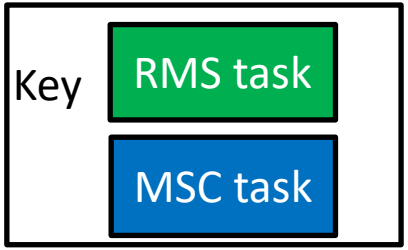
New Clinical Trial Application - Part I

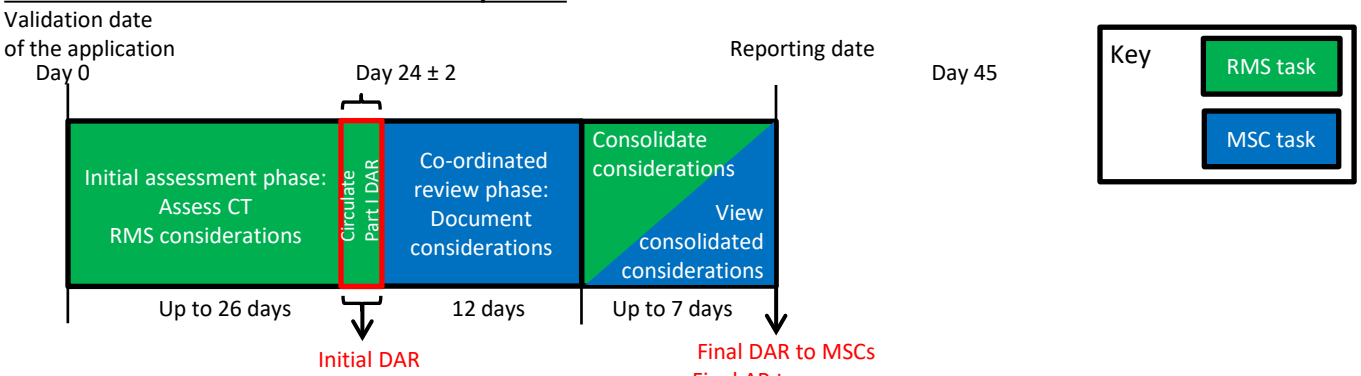
Assessment Timelines without RFI to sponsor



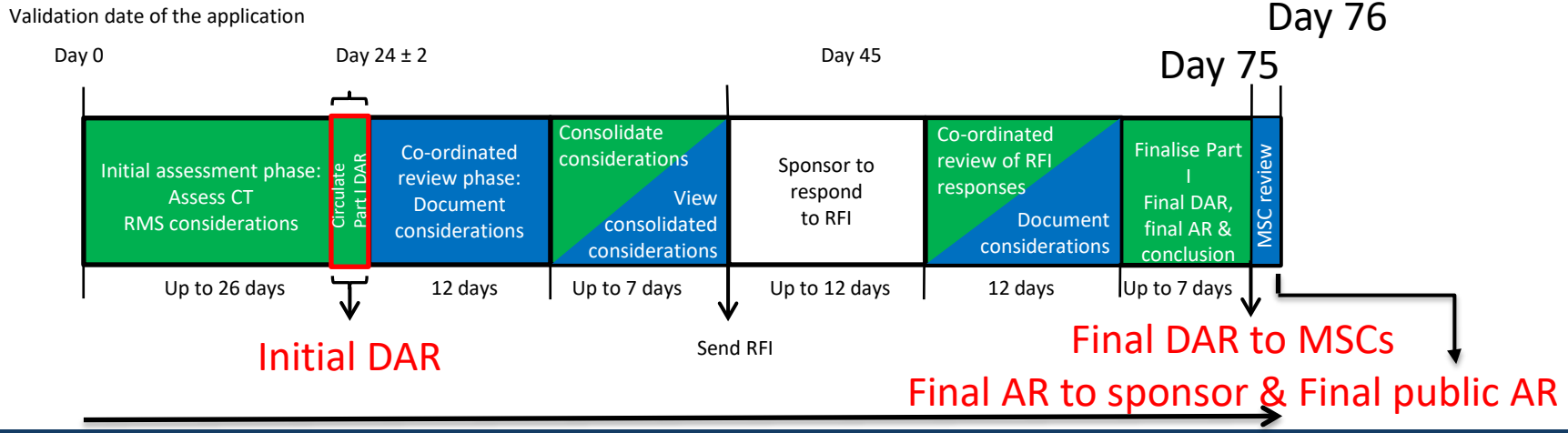


New Clinical Trial Application - Part I

Assessment Timelines without RFI to sponsor

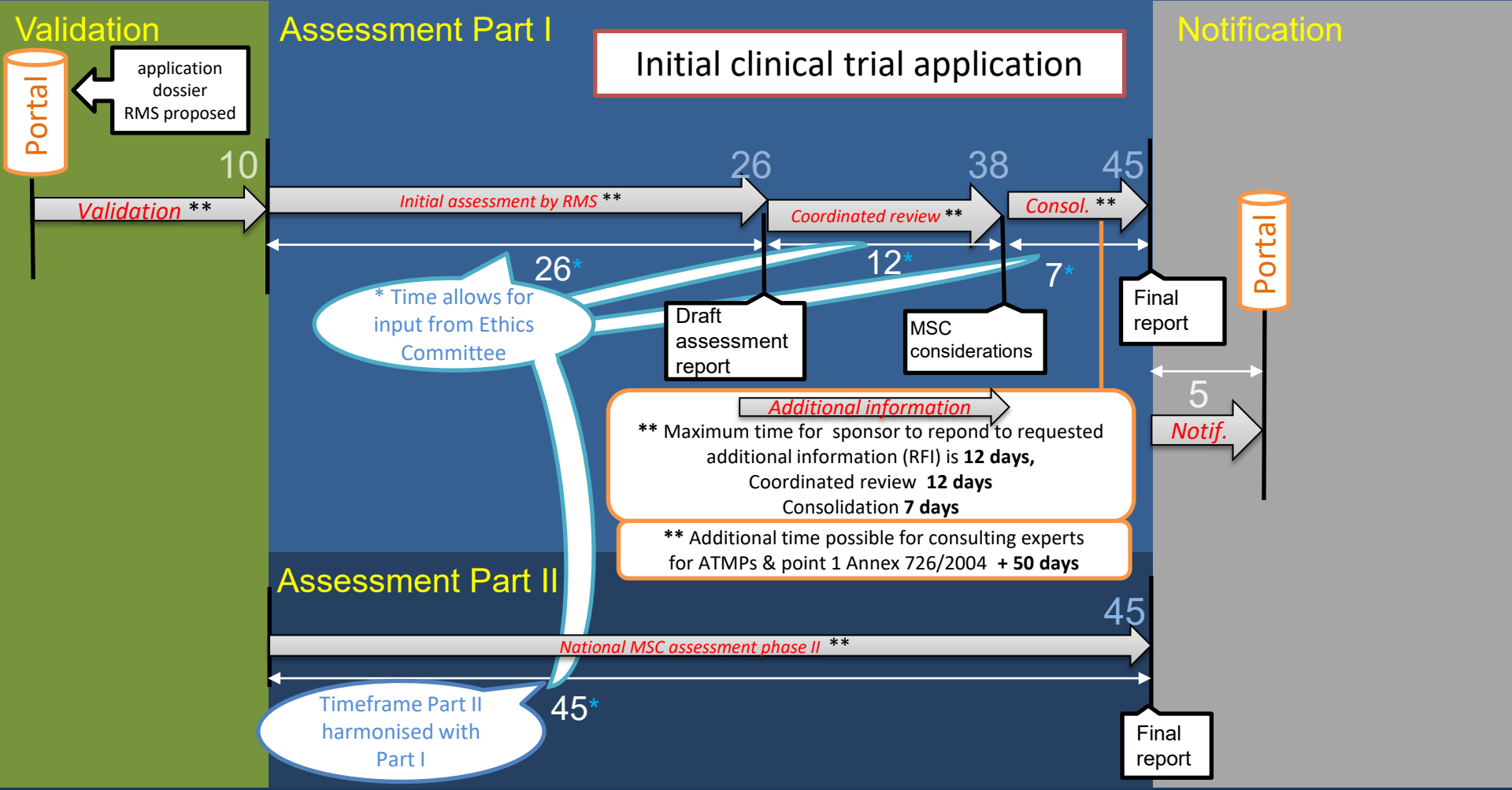


Assessment Timelines with RFI to sponsor



Extension of assessment - up to 50 days

- Only for **advanced therapy investigational medicinal product** - Regulation (EC) No 1394/2007 **- and medicinal products defined in point 1 Annex of** Regulation (EC) No 726/2004
- Such extensions apply to any *assessment phase* as decided by RMS
- Extended assessment could include both additional days for the RMS and MSCs and must always be clearly communicated by the RMS before implemented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** Maximum time for sponsor to repond to requested additional information (RFI) is 12 days,
Coordinated review 12 days
Consolidation 7 days
** Additional time possible for consulting experts for ATMPs & point 1 Annex 726/2004 + 50 days
Assessment Part II
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National MSC assessment phase II **
Timeframe Part II harmonised with Part I
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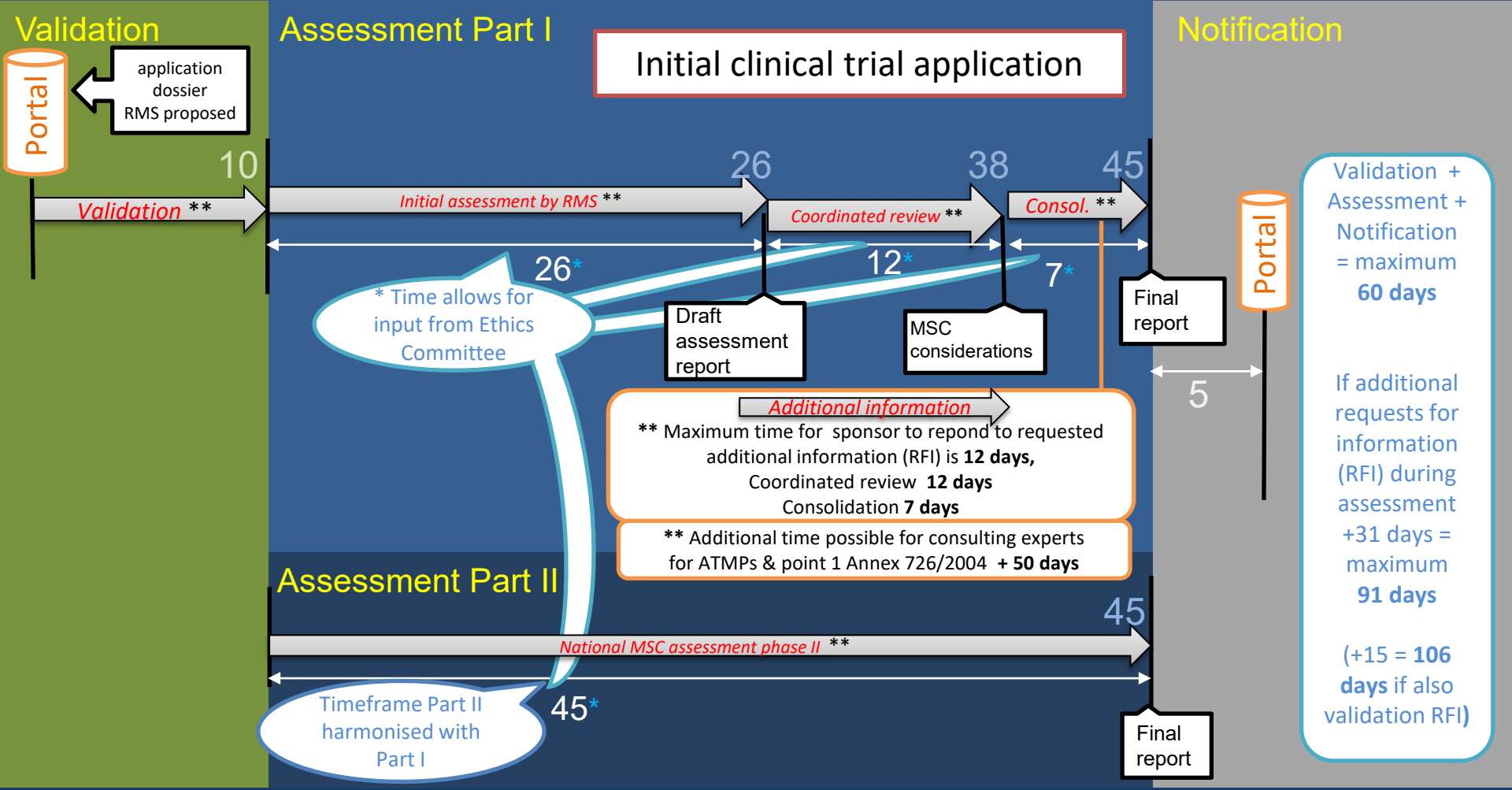
Final report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Final report
Validation + Assessment + Notification = maximum 60 days
If additional requests for information (RFI) during assessment +31 days = maximum 91 days
(+15 = 106 days if also validation RFI)

Timelines must be followed by sponsor and RMS

- Application lapses if no response/additional information in time
- Tacit validation if no active decision in time
- Maximum timelines in legal text - RMS in control
  - Best practise = RMS provides maximum time (12 days) for sponsor to answer RFI and full time (12 days) to MSCs for the ’coordinated review’ phase
  - timelines shortened for ’coordinated review’ when all MSCs provided input through ’complete’ tickbox in the Portal

DAR versions Part I - and final AR (FAR)

- **one initial Draft Assessment Report** Day 26 (word format)
- **one final Draft Assessment report**, preferably circulated one day before the upload of the Final Assessment Report to the Portal (and sponsor) (word)
- Tool to facilitate deletion of the final Draft Assessment Report ’work space boxes’ containing confidential information (word) to generate the Final Assessment Report (pdf)
- Note that the Public version of the Final Assessment Report (pdf) does not contain the Quality part of the Final Assessment report (=but this section sent to sponsor at the reporting date)

Timing of DAR circulation - best practise

- **The following principles** have been agreed as **Best Practise** for **timing** of **DAR circulation**
- **Predictability** when ***coordinated review phase* will *start* and *end*** are key for RMS-MSC interaction in multinational trials

For a new trial application: A DAR should be uploaded by the RMS to the Portal 24 (± 2) days after validation, i.e. not earlier than Day 22 and not later than Day 26 of the assessment phase

- If early = notification to MSCs
- If later than Day 26 - alert to MSCs

Late DAR

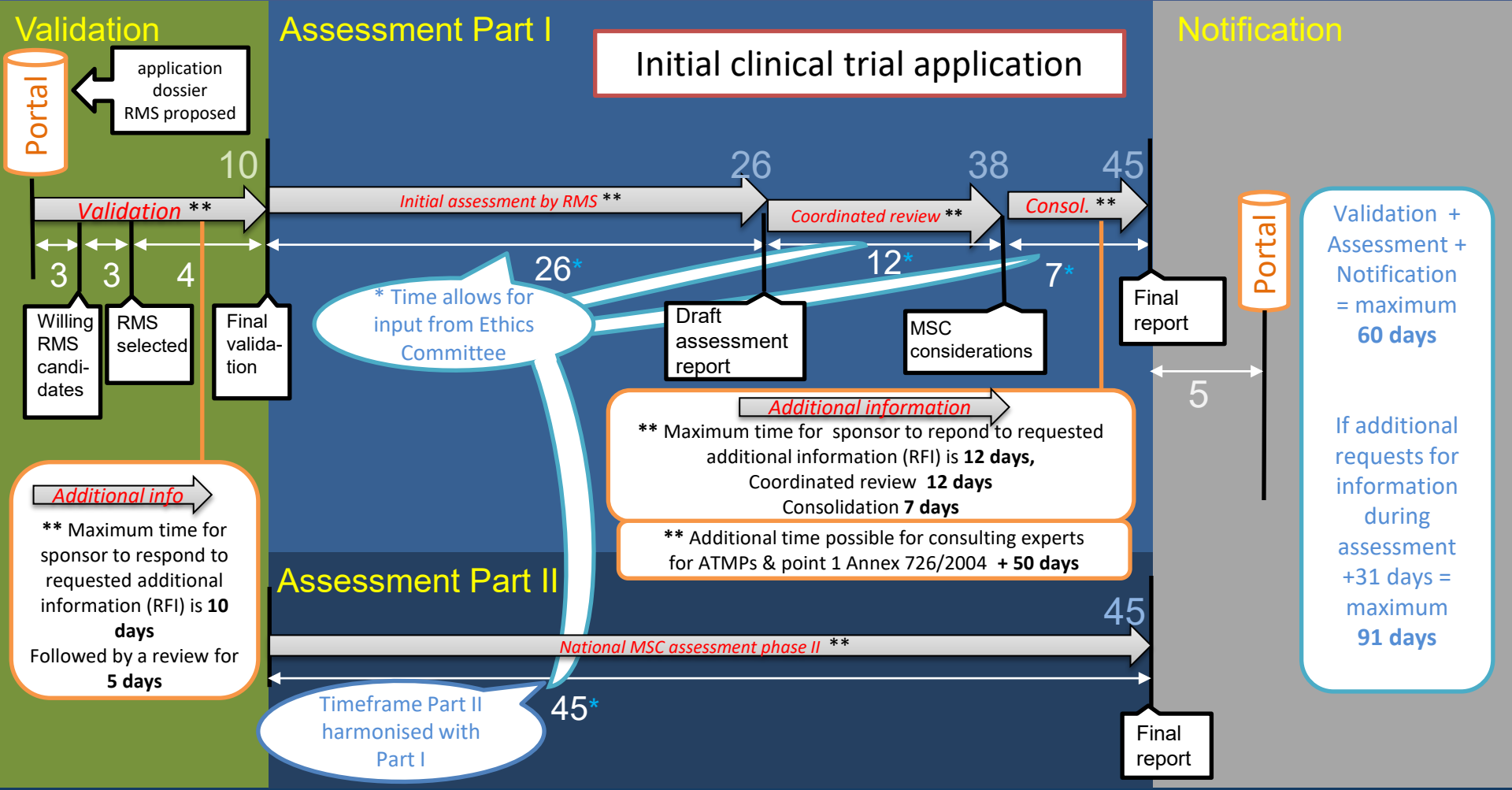
- If *later than legal obligation (>Day 26) due to unforeseen circumstances*, efforts by RMS to circulate DAR *at the latest Day 28 - alert about the delay communicated to all MSCs*
- *Any overdue delivery of the DAR must not infringe on the legally defined time for review by MSCs* to provide considerations (12 days)
- No change in total length of assessment phase = unexpected delays by the RMS result in shortened time window for RMS consolidation (as an example, in case of 2 days late DAR delivery (Day 28), the consolidation phase will be reduced with 2 days from 7 to 5 days)

Very late DAR

- If *no DAR circulated Day 29*, *all MSCs recommended to contact the RMS to find out reason for the unacceptable late delivery*
- Efforts to avoid that sponsor suffers from inadequate RMS conduct
- Sponsor may prefer withdrawal and resubmission of initial application to ensure predictable behaviour with a new RMS fulfilling the responsibilities according to regulation

Too late DAR - Critical situations not anticipated by the regulation

- If **no DAR is delivered by Day 32**, MSCs should initiate a discussion on how to proceed. An immediate solution must be presented by the RMS. MSCs to consider rejecting the trial application
- Similarly, if **a final AR and a conclusion is uploaded to the Portal without any prior circulation of a DAR** (with or without RFIs to sponsor), this infringes on MSCs legal right to review what was initially assessed and documented by the RMS. MSCs to consider rejecting the trial application
- RMS could be held accountable to sponsor


Validation
Assessment Part I
Notification
Initial clinical trial application
Portal
application dossier RMS proposed
10
26
38
45
Validation **
Initial assessment by RMS **
Coordinated review **
Consol. **
3
3
4
26*
12*
7*
Willing RMS candi-dates
RMS selected
Final valida-tion
* Time allows for input from Ethics Committee
Draft assessment report
MSC considerations
Final report
Portal
5
Additional info
** Maximum time for sponsor to respond to requested additional information (RFI) is 10 days
Followed by a review for 5 days
Additional information
** Maximum time for sponsor to repond to requested additional information (RFI) is 12 days,
Coordinated review 12 days
Consolidation 7 days
** Additional time possible for consulting experts for ATMPs & point 1 Annex 726/2004 + 50 days
Validation + Assessment + Notification = maximum 60 days
If additional requests for information during assessment +31 days = maximum 91 days
Assessment Part II
45
National MSC assessment phase II **
Timeframe Part II harmonised with Part I
45*
Final report

Thanks for your attention!
Questions welcome…

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