The BE CTR pilot project

DG pre, R&D

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Anne Lenaers

famhp
federal agency for medicines and health products

.be

Agenda

1. Pilot project procedure updates
2. Pilot figures
3. Lessons learned
4. Feedbacks from the surveys
5. Notifications
6. Further steps and conclusion
7. Questions?

1. Pilot project procedure updates

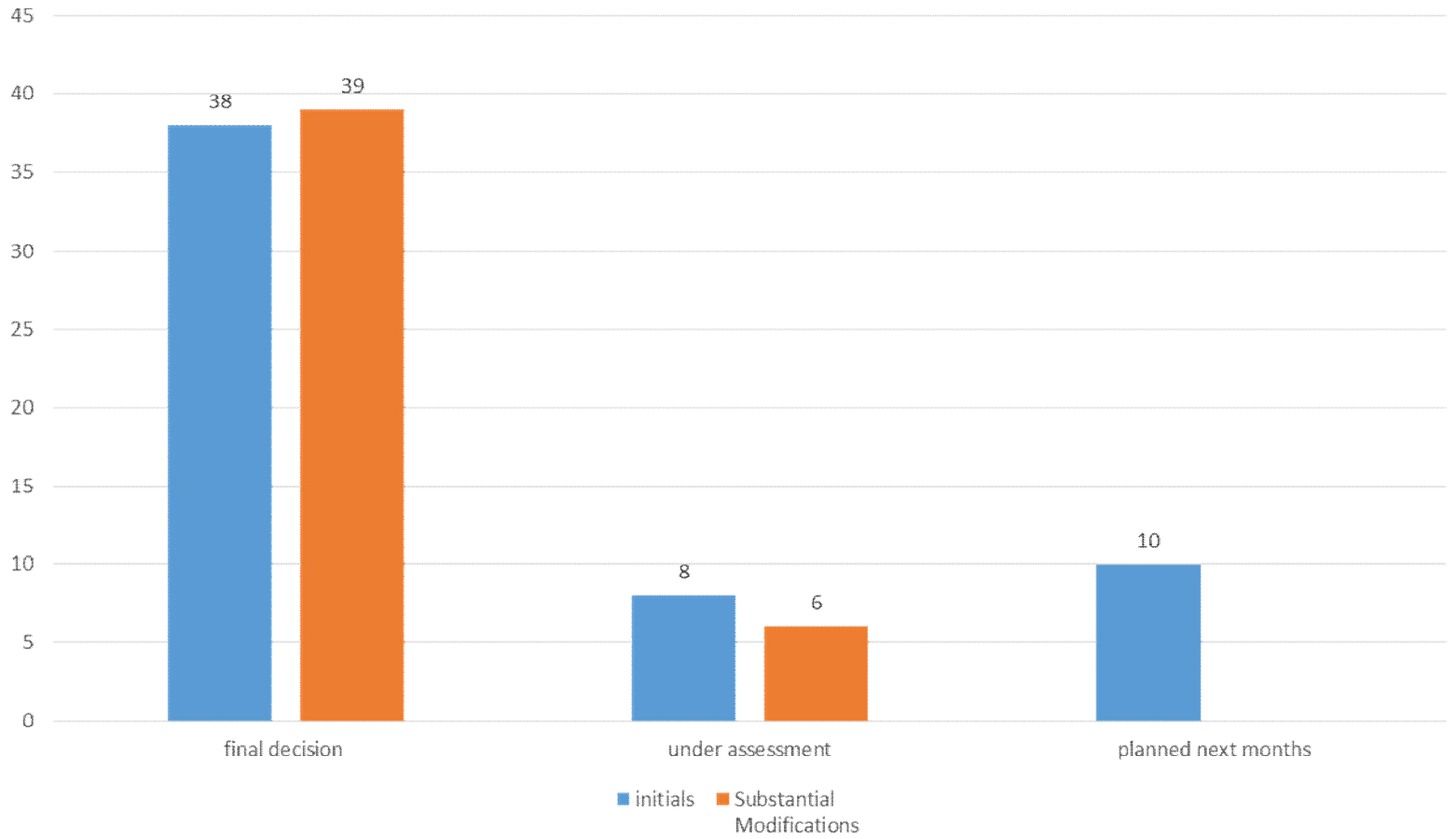
- **Fifth version** of the CTR pilot guidance for sponsors available on FAMHP website: https://www.afmps.be/sites/default/files/content/ctr_pilot_project_guidance_for_sponsors_v5.0_16-11-2018_7.pdf

- Main changes :
  - New version of the letter of intent.
  - Clarification of the role of the site in the submission process *****
  - Submission via CESP only since October 2018.
  - Clarification of timelines for phases I and mixed phases I/II and CTA/Substantial Modifications with ATMPs.
  - Clarifications related to protocol (synopsis and termination criteria).
  - Protection of the data statement following GDPR.
  - Addition of a site not possible before 3 months after approval of initial.

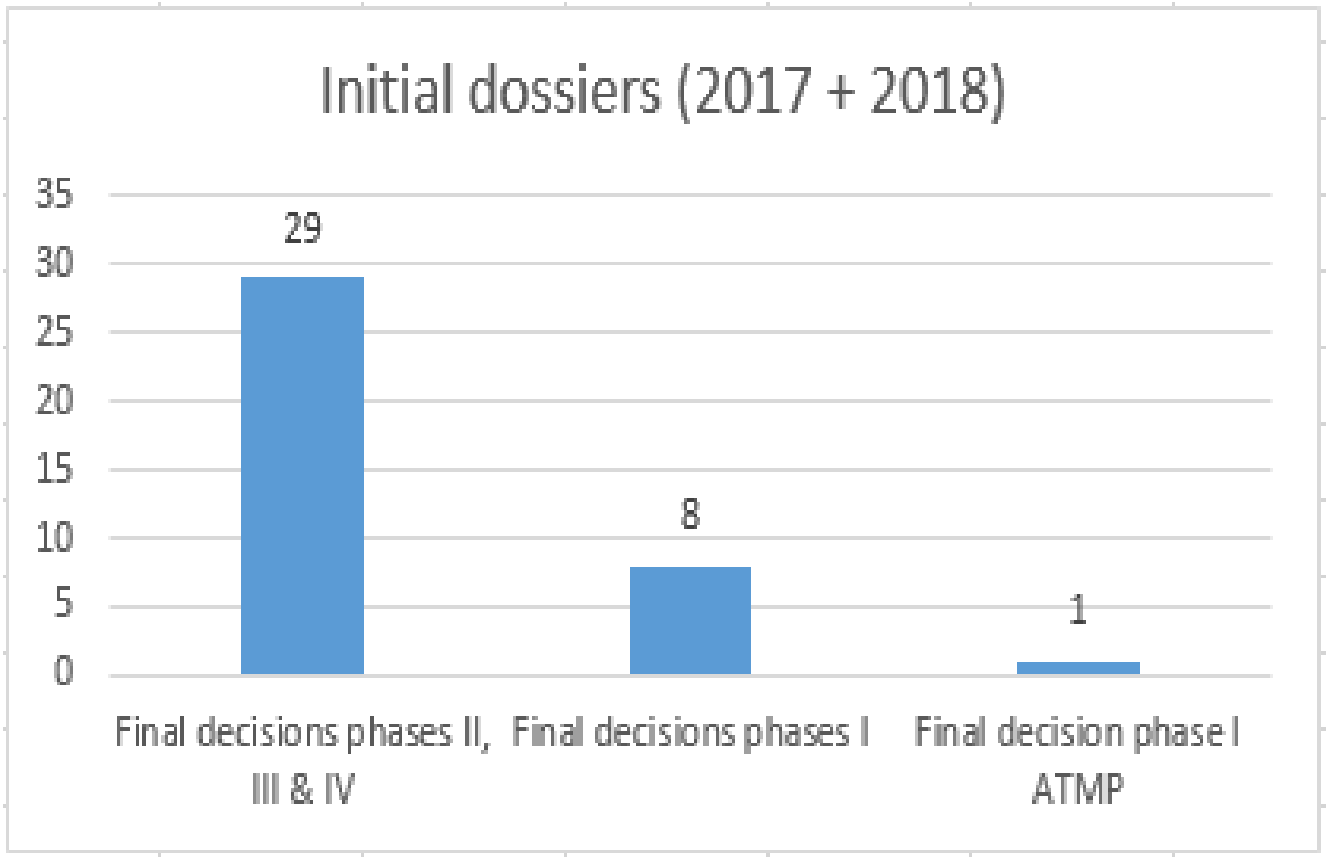
***** Post meeting note : each site receives the initial submitted dossier and the approval letters (with versions numbers of the finalised documents) from the College, not the finalised documents.

2. Pilot figures

Global overview pilot dossiers (2017 + 2018)

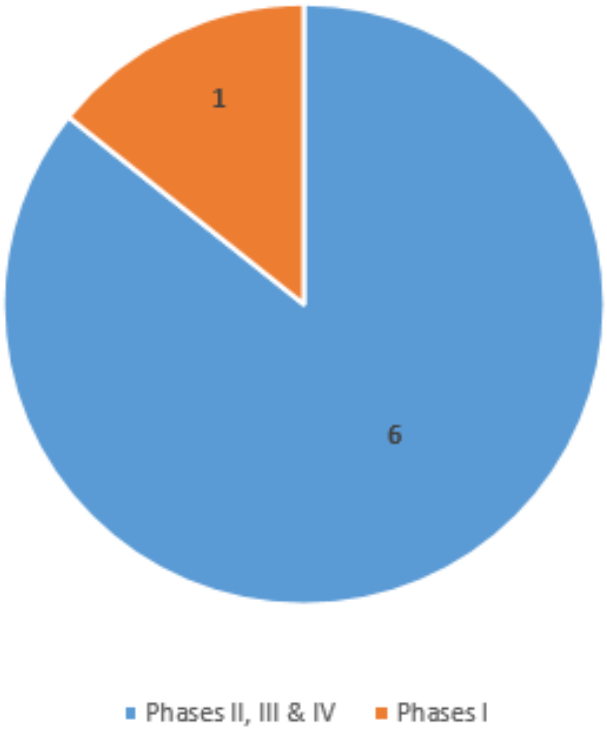


2. Pilot figures

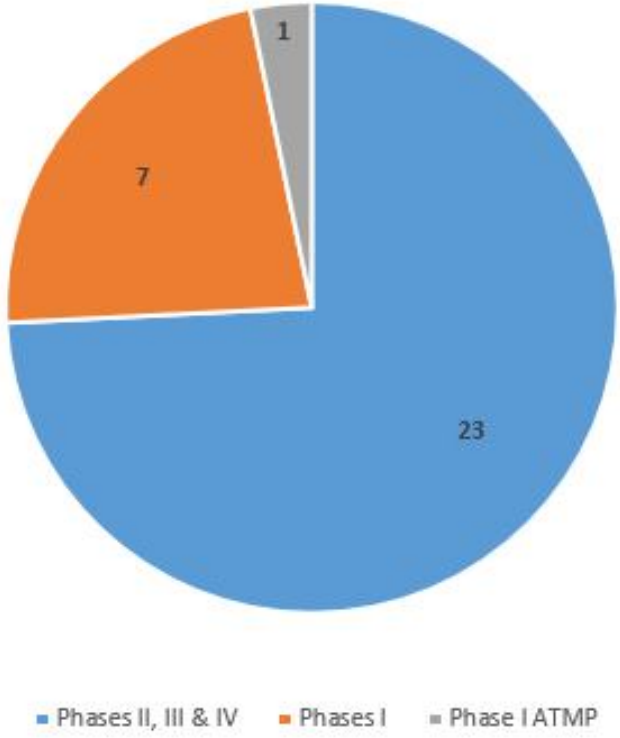


2. Pilot figures

finalised Pilot initials in 2017 (**7 dossiers**)

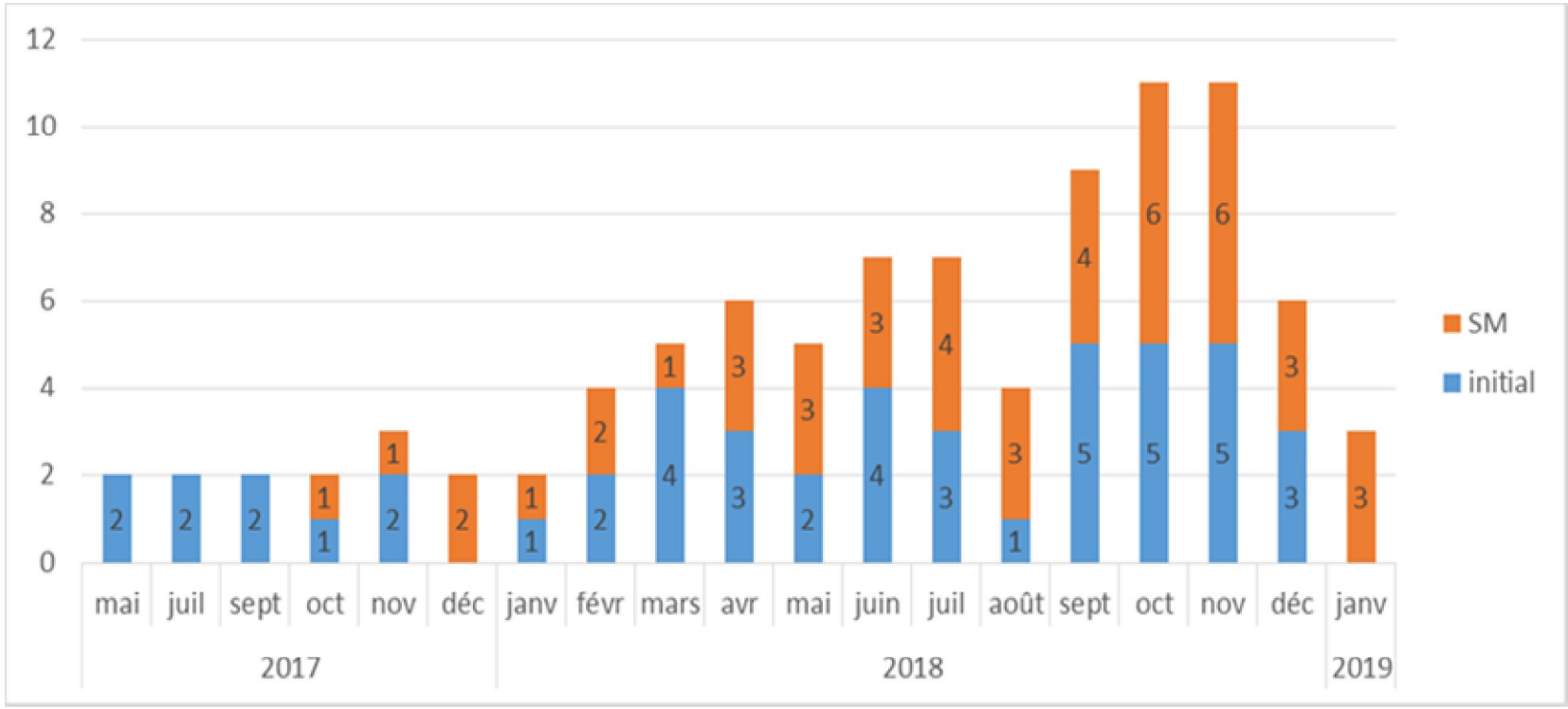


finalised Pilot initials in 2018 (**31 dossiers**)



2. Pilot figures

Evolution of the pilot submissions



Mean timeline between submission and final conclusion (as presented at the BRAS meeting in September 2018)

Timeline from reception to final conclusion (data 26/3/2018)

	#	Max timeline (procedure): From reception until final conclusion	# within	# without	Average timeline (real)
Initial					
phase I	**2**	47	1	1	51
phase II-IV	**9**	65	7	2	58
SM					
phase II-IV	**6**	61	6		34

Timeline from reception to final conclusion (data 3/9/2018)

	#	Max timeline (procedure) : from submission until final conclusion	# within	# without	Average timeline (real)
Initial					
phase I	**5**	47	4	1	39
Phase I ATMP	**1**	77	1	0	66
phase II-IV	**19**	65	17	2	56
SM					
phase II-IV	**21**	61	21	0	29

2. Pilot figures

Mean timeline between submission and final decision : update

Timeline **from reception to final conclusion** (**data 03/09/2018**)

	#	Max timeline (procedure) : from submission until final conclusion	# within	# without	Average timeline (real)
Initial					
phase I	**6**	47	5	1	**39**
Phase I ATMP	**1**	77	1	0	66
phase II-IV	**21**	65	19	2	**56**
SM					
phase II-IV	**24**	61	24	0	**29**

Timeline **from reception to final conclusion** (**data 31/12/2018**)

	#	Max timeline (procedure) : from submission till final conclusion	# within	# without	Average timeline (real)
Initial					
phase I	**8**	47	7	1	**38**
Phase I ATMP	**1**	77	1	0	66
phase II-IV	**29**	65	26	3	**54**
SM					
Phases II, III & IV	**35**	61	35	0	**29**
Phases I	**2**	47	2	0	23
Phases I ATMP	**2**	77	2	0	24

2. Pilot figures

Mean total timeline (between submission and final decision or all conditions met)

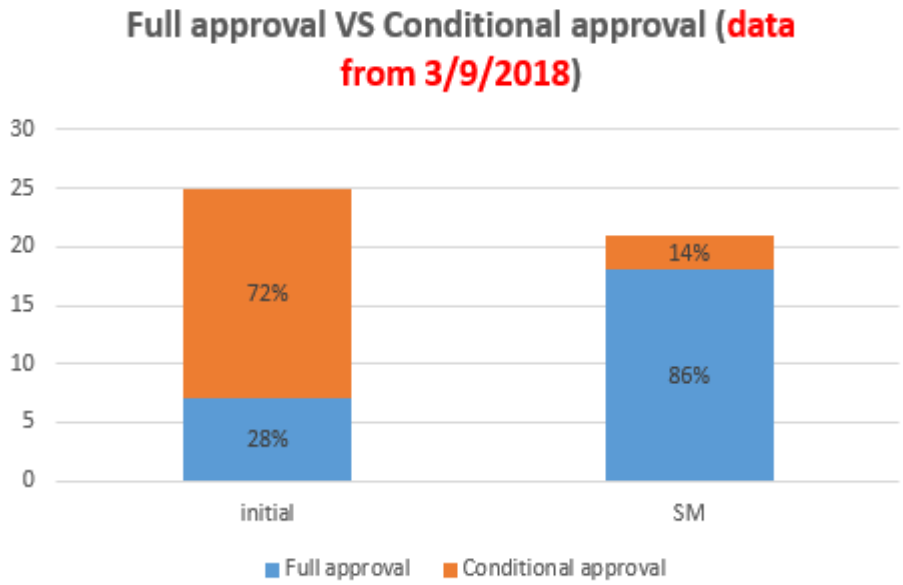
Total timeline (data 03/09/2018)

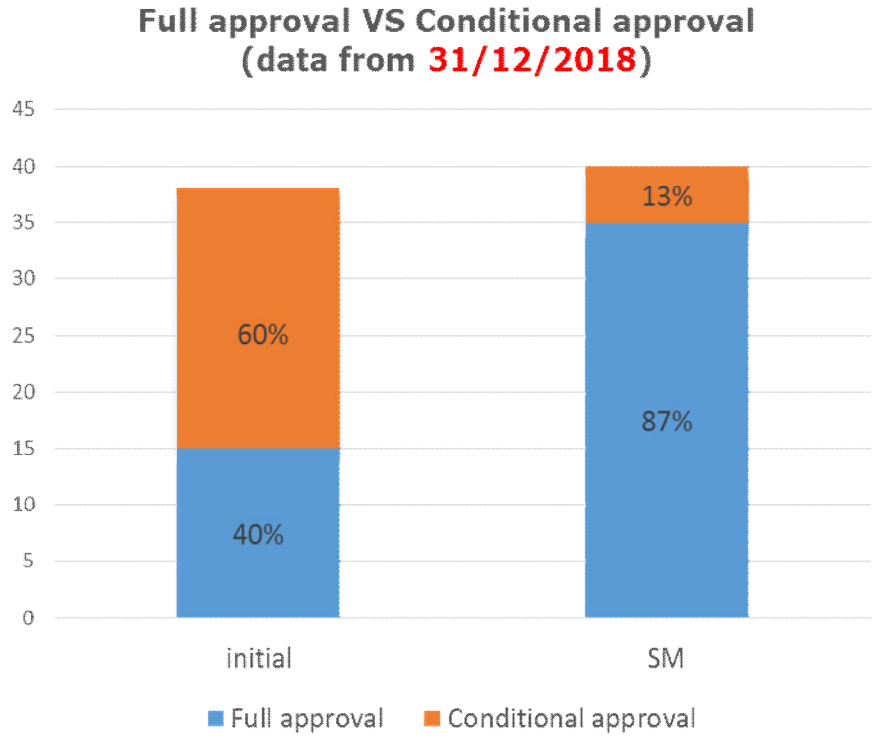
	#	Average timeline to issue the final decision	Average timeline to have all conditions met
Initial			
phase I	**5**	39	**60**
Phase I ATMP	**1**	66	66
phase II-IV	**19**	56	**66**
SM			
phase II-IV	**21**	29	**30**

Total timeline (data 31/12/2018)

	#	Average timeline to issue the final decision	Average timeline to have all conditions met
Initial			
phase I	**8**	38	**54**
Phase I ATMP	**1**	66	66
phase II-IV	**29**	54	**62**
SM			
phase II-IV	35	29	**36**
phase I	2	23	23
Phase I ATMP	2	23	23

2. Pilot figures





3. Lessons learned

Submission

- Structure of the dossier : folders name have been shortened in the empty structure zip file to avoid technical errors when saving documents in each folder => please avoid an additional level in the zip (part I and part II directly zipped and not a file containing part I and part II).

3. Lessons learned

Validation

- The mean time for validation was 10 days for initial trials at the end of 2018 (max timeline is 25 days in the pilot procedure)

- However this could be less as we remark that we often send the same questions :
  - Written statement (not provided or incomplete)
  - Recruitment procedure missing
  - Inform consent procedure missing
  - CV of the investigator : GCP training can be included or separated
  - GDPR statement
  - Separate synopsis of the protocol

3. Lessons learned

Evaluation (reminder)

Part I

- ✓ Clinical trial termination criteria should be included in the protocol. A section/paragraph should state that the sponsor has the right to terminate the study at any time and define reasons for the termination of the study prematurely (e.g. incidence or severity of adverse events indicates a potential health hazard for patients, patient enrollment is unsatisfactory, poor protocol adherence etc.).
- ✓ The DSMB charter (at least draft version) must be provided if a DSMB is foreseen for the trial.
- ✓ Adequate arrangements should be available in the protocol to secure data compliant with GDPR.
- ✓ Please pay attention to CTFG's "Recommendations related to contraception and pregnancy testing in clinical trials" when preparing the protocol.
- ✓ IB : the RSI section should be written according to the recommendations of the CTFG – Q&A document on RSI.

Part II

- ✓ ICF : please pay attention to the translations, consistency with protocol and other trial documents and compliance with GDPR

3. Feedbacks from the surveys

- Recurrent feedback : it sometimes takes very long to obtain the written statements (suitability statement) from the site.

- RFI letter : not clear if we are required to give additional information in a separate document or if an amendment of the actual study documentation (for example protocol) is needed.

- From the RFI letter it wasn't clear which questions for part I came from the EC and which came from the FAMHP.

5. Notifications

- Different categories of document can be provided to the NCP after the approval of the initial trial.

- Sometimes it is not easy to know what has to be provided, how and when.

=> We listed all possible documents that are sent by the applicant to the NCP in the context of the CTR pilot project.

5. Notifications

CTR pilot : all possible types of documents that can be submitted by the applicant to the NCP
A. Submissions related to the approval process of an initial trial dossier (from TS)
CTA package following annex I of CTR
Answers to the validation questions if applicable (only for FAMPH)
Answers to the RFIs if applicable
Answers to the condition(s) if applicable
B. Submissions related to the approval process of a substantial modification (from TS) : e.g. new ICF versions, New patients diaries, intervention of recruitment assistants (new recruitment procedure)
SM package following annex II of CTR
Answers to the validation questions if applicable (only for FAMPH)
Answers to the RFIs if applicable
Answers to the condition(s) if applicable
C. Notification of Urgent Safety Measures (where an unexpected event is likely to seriously affect the benefit-risk balance)
Can be implemented without waiting for autorisation but shall be notified not later than 7 days from the implementation
D. Notification of temporary halt of the trial or of recruitment only (can be the result of an USM)
EU application form for SM, completed with date of halt of the CT and reason why / restart only after submission of an SM
E. Notification of the end of trial
Declaration of the end of trial form
F. Notifications that have to be sent immediately
Proof of insurance renewal
Notification of a general precaution further to the release of drug safety communication if not an USM or temporary halt (e.g. Dear Investigator Letter)
Yearly Status of the study. This notification is normally done in January or at the birthday date of EC study approval
G. Notifications that do not have to be sent immediately and can be added to the next substantial modification
Signed version of approved documents (e.g. protocol, finalised contracts)
Translated version of approved documents (e.g. patient diary, ICF, …)
Evolution report at time of moving from one cohort to another cohort in the study
Protocol clarification letter related to non substantial changes
Typo's
Removal of one or several sites
H. Notification of the summary of the results [Clinical Study Report (CSR) or synopsis of the CSR]
Should be submitted within one year from the end of a clinical trial in all Member States concerned

5. Notifications

Examples

- **Substantial Modifications (SMs)** :

e.g. new ICF versions, new patient diaries, intervention of recruitment assistants (new recruitment procedure).

- **Documents that are not SMs but have to be sent immediately to the NCP** :

e.g. proof of insurance renewal, notification of a precaution further to the release of a drug safety communication which is not an USM or a temporary halt (e.g.: DIL), yearly status of the study.

5. Notifications

Examples

- **Notifications that must be sent at the occasion of the next substantial modification :**

E.g.:

- Signed versions of approved documents (e.g.: protocol, finalised contract)
- Translated versions of approved documents (e.g.: patient diary, ICF, ...) **Post meeting clarification** : it is to be noticed that in the initial submission, ICFs must be provided in the language**s** of the participants (e.g. FR and NL). However, comments from the EC will be given in one language (e.g. NL) => the adapted ICF has to be provided in this language before approval of the initial trial. The translated adapted ICF(s) (in FR in the example) may be provided later at the occasion of the next SM.
- Evolution report at time of moving from one cohort to another cohort in the study
- Protocol clarification letter related to non substantial changes
- Typos
- Removal of one or several sites

5. Notifications

- This list is a living document and will be completed with other examples when available.

- It will be added to the next update of the Pilot procedure for sponsors.

6. Further steps and conclusion

- We will continue to update and fine tune the processes taking your feedbacks into consideration.

- In order to enlarge possibilities in the pilot, we would like to include VHP dossiers in the process.

6. Further steps and conclusion

- Our proposition would be a VHP plus process :
  - ° with the part I of the dossier submitted to the VHP-A
  - ° and the part II of the dossier submitted to the BE NCP
  - ° Both submissions (part I and part II) would be pre-submissions (principle of the VHP)
  - ° National legal submission of both parts would occur after the end of the VHP process.
  - ° Approval would be an administrative approval for both parts, within 10 days.

- Details of the Pilot VHP plus process have still to be discussed/fine-tuned with the ECs in the pilot work-group.

- Some flexibility could be foreseen for the moment of submission of some documents in part II.

6. Further steps and conclusion

- Thanks a lot for your collaboration and participation.

- Please continue or give it a try : this is the only way to train the conditions of the CTR and to learn by doing.

- Please use our Pilot general e-mail address : CTRpilot@fagg-afmps.be

7. Questions ?

- Do you have questions ?

- Don’t hesitate to send us your questions to CTRpilot@fagg-afmps.be

Thank you very much for your attention

Contact

Federal Agency for Medicines and Health Products – FAMHP

Victor Hortaplein - Place Victor Horta 40/40
1060 BRUSSELS

tel. + 32 2 528 40 00
fax + 32 2 528 40 01
e-mail welcome@fagg-afmps.be

www.famhp.be

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