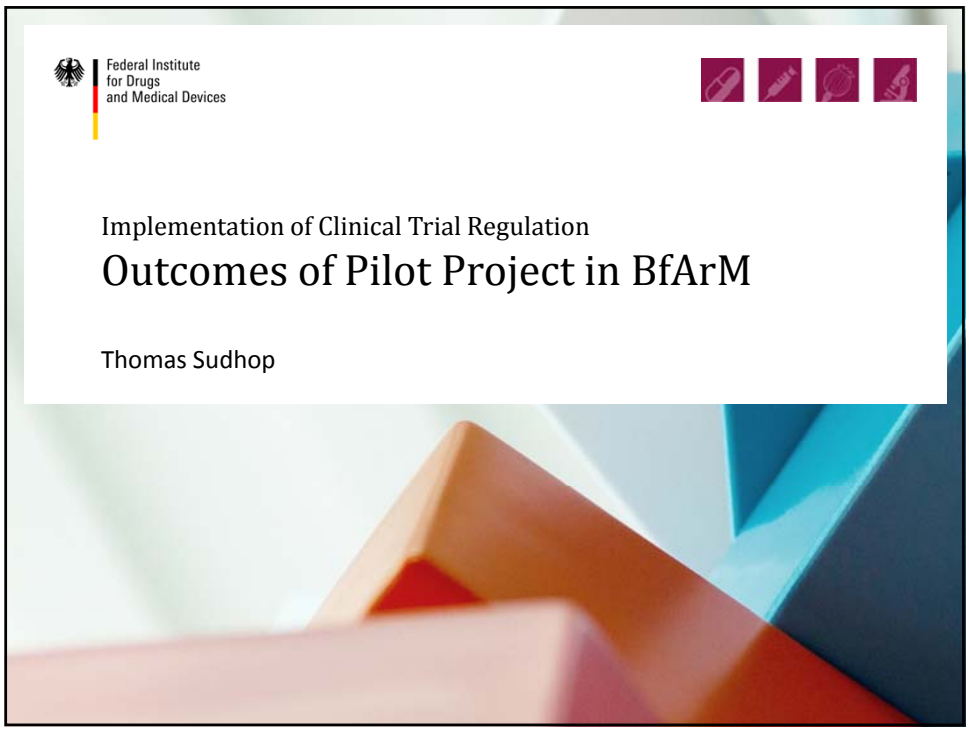

Situation prior 2015

- Under the current German legal situation, the procedures at ethics committees (EC) and national competent authorities (NCA [BfArM/PEI]) are strictly independent from each other
- No experience of joint assessments so far
- Public discussions on the new national legislation made it early clear that the system of multiple ECs would be maintained in Germany also under the new clinical trial regulation (CTR) and a close cooperation would become necessary
- Therefore, BfArM started a discussion with the working group of the German ECs in 2014/2015 on joint assessment of clinical trial applications (CTA)

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Intentions

- The Pilot Project is intended to simulate **processes and deadlines** of the CTR in the context of current active CTAs
- Intended as "boot camp" for
  - German competent authorities (BfArM & PEI)
  - German ethics committees
  - Applicants of mono-national CTAs
- "Not a drill" approach
  - New active CTA are jointly assessed under "real live" conditions
  - using CTR procedures foreseen for the assessment of Part I of the dossier
  - resulting in legal binding decisions

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Objectives of the Pilot Project

- Process design for the joint assessment of Part I of a CTA by EC and NCA
- Implementation within the framework of the (current) legal approval procedure according to the German Medicinal Product Act (AMG) and the German GCP Ordinance (GCP-V)
  - Legally secure procedure
  - Evaluation of active (current) CTAs, no "dummy" applications
- Deadlines in accordance with CTR when acting as reporting Member State
  - As far as currently legally possible
- Preparation of an internal assessment report
  - Based on VHP assessment report template
- Extensive consideration of the new national rules (anticipated at the time)

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CTA Parts according CTR

- Separation of the contents of a current CTA in accordance with Part I and II of Articles 6 and 7 of the CTR (as far as possible according to AMG and GCP-V)
  - Part I: Protocol, Investigator's brochure (IB), IMPD
  - Part II: Informed consent, data protection, insurance, suitability of investigators and centres ...
- Joint validation of the CTA according to Section 7 subsection 1 and 2 GCP-V
- Joint assessment of the content of Part I (except IMPD: NCA only)

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Official Notifications

- Validation notice issued in parallel by EC and NCA
  - Identical text in both notifications
    - *In principle:* In accordance with Part I of the EU Regulation
    - *De facto:* According to Section 7 GCP-V
  - Different validation objectives according to Section 7 subsection 3 and 4 GCP-V
- The same principle also applies to shortcomings during scientific assessment
- Parallel dispatch of the letters of deficiencies by NCA and EC (also containing issues on Part II)
- Responses from the sponsor to both institutions in parallel
- Final notices will be sent separately from both institutions (for legally secure reasons)

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Deadlines

- Validation and assessment including remedy of deficiencies/re-delivery by the sponsor within the deadlines of the CTR
  - But: Exceeding the deadlines of the CTR does not lead to implicit (tacit) withdrawals or approvals
    - Unless this would also occur according to AMG/GCP-V
    - Neither for NCA, EC nor applicant (for subsequent deliveries)
    - Legally relevant are the deadlines according to AMG and GCP-V
- Deadlines are communicated to applicant and EC at the end of each pilot application by NCA and recorded in an internal statistic

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Process Management and concerned local ECs

- Process management done by the competent NCA (competent according to Section 77 AMG)
- Competent EC according to AMG (depending on the workplace of the coordinating investigator)
- Further concerned (local) ECs support the competent EC in such a way that deadlines can be met in accordance with the CTR
  - Consultation procedure between competent and concerned ECs
  - If the concerned EC does not provide assessment for the competent EC in time, the competent EC decides on its own

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Processes and Deadlines

Process (rough desc.)

- Sponsor sends **letter of intent** to NCA and competent EC with indented date of submission
- NCA and EC agree on **date of submission** (or drop out)
- **Sponsor submits CTA** in parallel to NCA and EC -> Pilot Procedure starts
- **NCA and EC jointly validate CTA**
    - EC also validates Part II
    - NCA validates IMPD (CMC part)
  - Result: Either valid application or request for additional documents
- If CTA valid: **NCA and EC jointly assess CTA** on Part I
- NCA and EC agree on a **common list of questions/objections** with regard to Part I (if any)
- NCA and EC jointly assess **additional information/comments** and come **to final conclusion**:
  - Agreement on decision or
  - Divergent opinions

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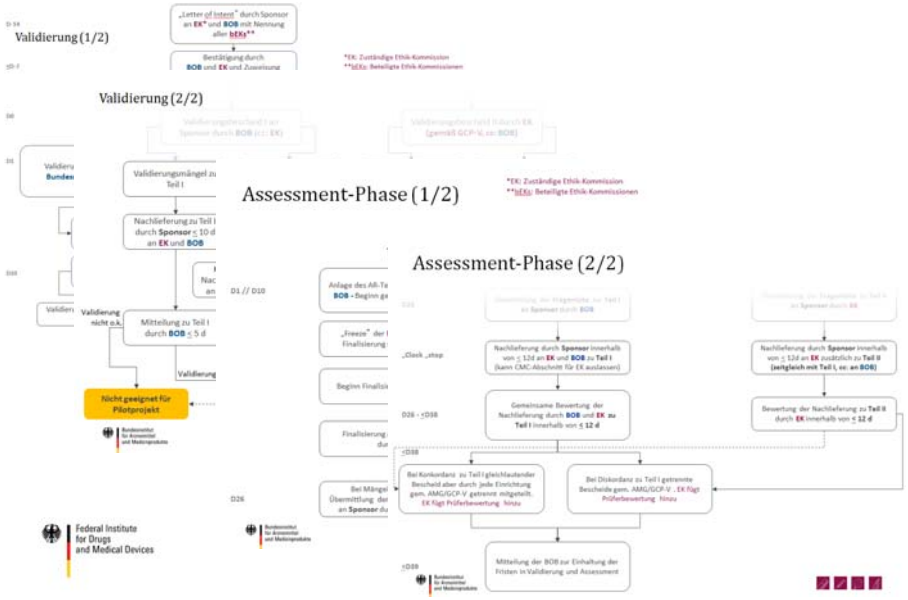
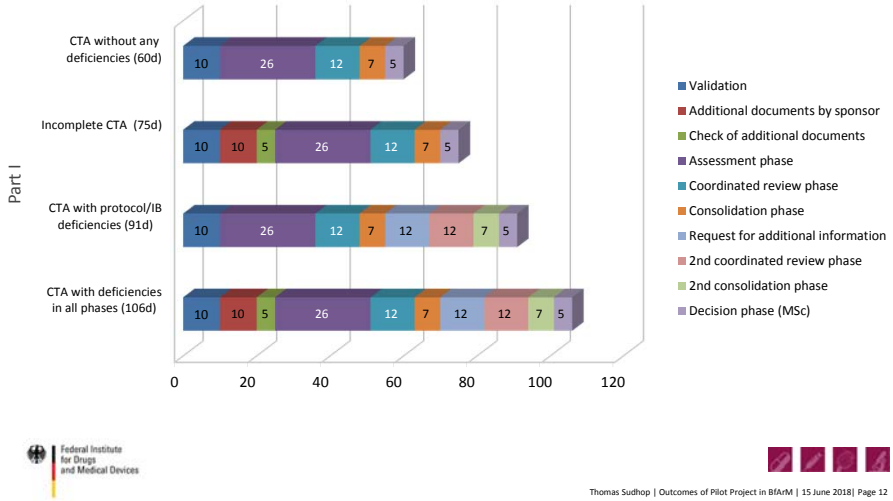
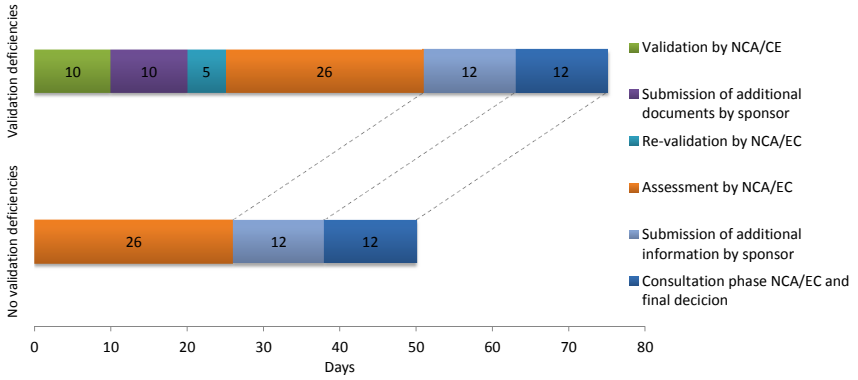
Internal SOPs (BfArM)



Deadline according to CTR



Deadlines of the Pilot Project



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Specifications

- Joint validation
  - Only check for existence of required documents as anticipated for the CTR
- Joint assessment limited to contents of Part I of the dossier except CMC aspects
  - Quality part of the IMPD is only submitted to the NCA but not to the EC in Germany
- Deadlines according to a mono-national rMS procedure with no other Member State concerned (MSc)
- No EU portal simulation
  - Paper bases submission as legally required, but
  - Follow-up communication by email or EUDRA-Link
- Separated decision or deficiencies letters by NCA and EC, but with the same wording with regard to Part I deficiencies

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Technical Requirements

- Use of a **collaboration suite** with an appropriate **rights and role management** to share information and assessment reports between the competent EC and the NCA not visible to not involved ECs
  - BfArM provides a MS SharePoint Server for information and document interchange
- Each participating EC got an **EUDRA-Link** account to receive additional information from the applicant
- **Monthly video and telephone conferences**
  - BfArM set up an Adobe Connect Server for communication purposes

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Implementation Process

- Process design for the cooperation between EC and NCA
- Assessment report template -> Use of VHP template
- SOP for ECs
- Guidance document for applicants (German / English)

- Advertising on homepages
- Go live: December 2015

- Change requests
  - Integration of substantial amendments

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Outcomes

Cooperation and Communication between ECs and NCAs

- Since March 2015 42 joint tele/video-conferences with NCAs and ECs
  - Currently monthly conferences
- Participating ECs
  - December 2015: 24 of 50 ECs
  - May 2018: 35 of 50 ECs
    - 11 at medical associations or ministries of the states (Länder)
    - 24 at medical faculties

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Distribution of Ethics Committees participating in the Pilot Project

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Participating Ethics Committees

EC at the **Baden-Württemberg** Medical Association	EC of the **Hamburg** Medical Association	EC at the **University of Regensburg**
EC at the Medical Faculty of the **Rheinische Friedrich-Wilhelms-University Bonn**	EC of the Medical Faculty of **Heidelberg**	EC of the **Rhineland-Palatinate** Medical Association
EC of the **Brandenburg** Medical Association	EC of the **Hesse** Medical Association	EC at the Medical Association of **Saarland**
EC of the **Bavarian** Medical Association	EC of the **Friedrich Schiller University Jena** at the Medical Faculty	EC of the **Saxon State** Medical Association
EC of the State of **Berlin**	EC of the Medical Faculty of the **Christian-Albrechts-University zu Kiel**	EC of the State of **Saxony-Anhalt** at the State Office for Consumer Protection Saxony-Anhalt
EC of the Medical Faculty of the **Ruhr-University Bochum**	EC of the Medical Faculty of the **University of Cologne**	EC at the **Schleswig-Holstein** Medical Association
EC at the **TU Dresden**	EC at the Medical Faculty of **the University of Leipzig**	EC of the Medical Faculty of the **Eberhard Karl University** and at the University Hospital **Tübingen**
EC of the Medical Faculty of the **Heinrich-Heine-University Düsseldorf**	EC of the **Otto-von-Guericke University** at the Medical Faculty and the University Hospital **Magdeburg**	EC of the **University of Ulm**
EC of the Medical Faculty of the **University of Duisburg-Essen**	EC of the Medical Faculty of **Ludwig-Maximilian University Munich**	EC of the Medical Association of **Westphalia-Lippe** and the **Westphalian Wilhelm University of Münster**
EC of the Medical Faculty **Friedrich-Alexander-University Erlangen-Nuremberg**	EC of the Faculty of Medicine of the **Technical University of Munich**	EC of the Medical Faculty of the **University of Würzburg**
EC of the Department of Medicine of the **Johann Wolfgang Goethe University Frankfurt**	EC of the **North Rhine** Medical Association	EC of the University Hospital Schleswig-Holstein **Campus Kiel University Children's Hospital**
EC of the Medical Faculty of the **Martin-Luther-University Halle-Wittenberg**	EC of the **Carl von Ossietzky University Oldenburg**	

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Ethics Committees with more than 3 Pilot Procedures

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Statistics since December 2015

- 110 „Letters of Intent“
  - 9 Procedures not accepted (1 by BfArM, 8 by ECs)
  - 1 Procedure withdrawn by sponsor prior submission
- 100 Procedures started (all BfArM)
- 73 Procedures finalised
  - 4 CTAs rejected

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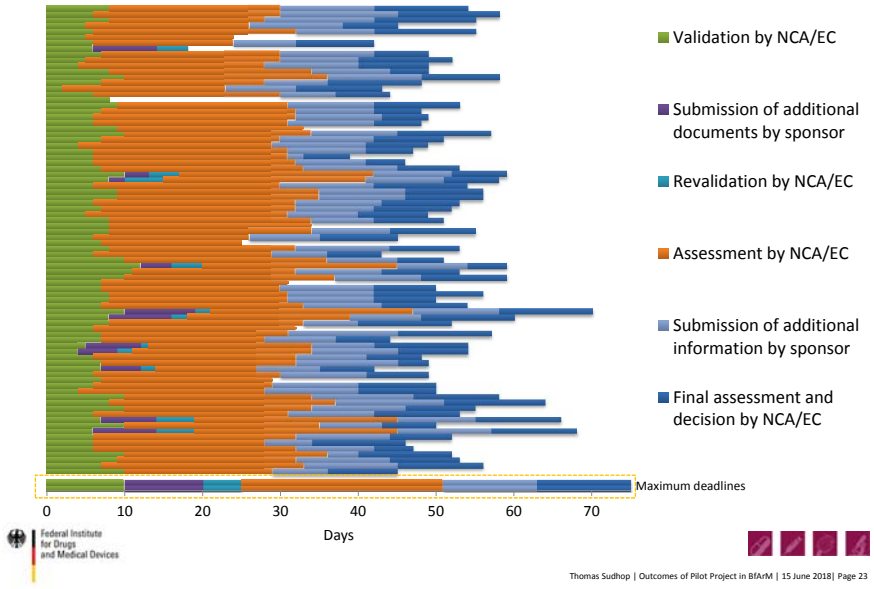
Duration of Procedures and Adherence to Deadlines



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Statistics of Sub-processes (days)

Sub-process	Mean	SD	Median	Min	Max	Legal deadline	Outliers
Validation by NCA/EC (n=86)	7.1	1.9	7	2	**12**	≤ 10	11, 12 **(2.3%)**
Submission of additional documents by the sponsor (n=11)	6.0	2.3	7	2	9	≤ 10	-
Re-validation by NCA/EC (n=11)	3.3	1.5	4	1	5	≤ 5	-
Joint assessment by NCA/EC (n=82)	23.9	2.5	24	13	**29**	≤ 26	27, 29 **(2.4%)**
Submission of additional information by the sponsor (n=74)	10.4	2.3	11.	2	**15**	≤ 12	2x13,3x14, 2x15 **(9.4%)**
Conclusion and final notification by NCA and EC (n=74)	9.3	2.4	9.5	4	14	≤ 12	4x13, 1x14 **(6.8%)**
Total procedure (n=73)	45.5	6.3	45	33	68	≤ 76	

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Thank you very much for your attention!

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