

Allgemeines zur Klinischen Prüfung II



AGES

Österreichische Agentur für Gesundheit
und Ernährungssicherheit GmbH

*Health. Nutrition. Safety.
Our Concern.*

Verpflichtungen des Sponsors während der Klinischen Prüfung

Häufige Fragen zur Klinischen Prüfung

SUSARs



Table CA 81: Number of SAEs/SUSARs received per institution

Institution I discarded	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	296.8	496.429	528	356.6	651.25	849.364	1928.917	2933.1875
Standard deviation	248.93	663.798	787.931	410.825	1029.439	1223.180	4144.802	6141.35513
Sample size EU	5	7	8	10	8	11	12	16

- **ICREL** was a one-year project financed by the European 7th Framework Programme. Collaboration of the Medical University of Vienna, ECRIN, EORTC, as well as the Hospital Clínic of Barcelona coordinated by EFGCP.
- Its aim was to **measure and analyse** the direct and indirect **impact of the Clinical Trials Directive 2001/20/EC** and related legislations in the EU on all categories of clinical research and on the different stakeholders: commercial and non-commercial sponsors, ethics committees and competent authorities.

http://www.efgcp.be/downloads/icrel_docs/ICREL_Appendix_CA.pdf

Dir 2001/20/EC Art 17

Berichte über schwerwiegende Nebenwirkungen

(1) a) Der Sponsor sorgt dafür, dass *alle wichtigen Informationen über mutmaßliche unerwartete schwerwiegende*

Nebenwirkungen, die zu einem Todesfall geführt haben bzw. führen können, aufgezeichnet und den zuständigen

Behörden aller betreffenden Mitgliedstaaten sowie der Ethik-Kommission so rasch wie möglich, auf jeden Fall aber *binnen sieben Tagen*, nachdem der Sponsor von dem betreffenden Fall Kenntnis erhalten hat, mitgeteilt werden und dass anschließend innerhalb einer *erneuten Frist von acht Tagen* entsprechende Auskünfte über die weiteren Maßnahmen übermittelt werden.

AMG §41e

Meldungen über schwerwiegende Nebenwirkungen

- (1) Der Sponsor hat dafür zu sorgen, dass alle wichtigen Informationen über mutmaßliche unerwartete schwerwiegende Nebenwirkungen, **die im Rahmen der selben klinischen Prüfung im Inland oder im Ausland** aufgetreten sind und die zu einem Todesfall geführt haben oder lebensbedrohlich sind, aufgezeichnet und dem Bundesamt für Sicherheit im Gesundheitswesen und den zuständigen Behörden aller Vertragsparteien des Europäischen Wirtschaftsraumes, in deren Hoheitsgebiet die klinische Prüfung durchgeführt wird, und den betreffenden Ethikkommissionen so rasch wie möglich, auf jeden Fall aber *binnen sieben Tagen*, nachdem der Sponsor von dem betreffenden Fall Kenntnis erhalten hat, mitgeteilt werden und dass anschließend *innerhalb einer erneuten Frist von acht Tagen* entsprechende Auskünfte über die weiteren Maßnahmen übermittelt werden.

Dir 2001/20/EC Art 17

b) *Alle anderen mutmaßlichen unerwarteten schwerwiegenden Nebenwirkungen* werden den betreffenden zuständigen Behörden sowie der betreffenden Ethik- Kommission so rasch wie möglich, auf jeden Fall aber binnen 15 Tagen von dem Zeitpunkt an gerechnet, zu dem der Sponsor zuerst davon Kenntnis erhalten hat, mitgeteilt.

AMG §41e

(2) Alle anderen mutmaßlichen unerwarteten schwerwiegenden Nebenwirkungen, **die im Rahmen der selben klinischen Prüfung im Inland oder Ausland aufgetreten sind**, sind den im Abs. 1 genannten Behörden sowie den betreffenden Ethikkommissionen so rasch wie möglich, auf jeden Fall aber binnen 15 Tagen von dem Zeitpunkt an gerechnet, zu dem der Sponsor zuerst davon Kenntnis erhalten hat, mitzuteilen.

Dir 2001/20/EC Art 17

AMG §41e

d) Der Sponsor unterrichtet hierüber auch die übrigen Prüfer.

(3) Der Sponsor hat auch den übrigen Prüfern der selben klinischen Prüfung **Informationen** im Sinne der Abs. 1 und 2 zu geben. Einmal jährlich während der gesamten Dauer der klinischen Prüfung hat der Sponsor den im Abs. 1 genannten Behörden und den betreffenden Ethikkommissionen eine Liste mit allen mutmaßlichen schwerwiegenden Nebenwirkungen, die während der gesamten Prüfungsdauer aufgetreten sind, sowie einen Bericht über die Sicherheit der Prüfungsteilnehmer vorzulegen.

AMG § 28. (2) Die Planung und Durchführung klinischer Prüfungen hat unter Einhaltung der Vorschriften dieses Bundesgesetzes entsprechend dem Stand der Wissenschaften und nach den **Grundsätzen guter klinischer Praxis** zu erfolgen. Zur **Auslegung der Grundsätze** guter klinischer Praxis sind die allgemein anerkannten Grundsätze und Anforderungen heranzuziehen, die in **Band 10** der Regelungen der Arzneimittel in der Europäischen Gemeinschaft veröffentlicht sind.

The sponsor is responsible

- ...the **prompt notification** to all concerned investigator(s), the EC and CA of each concerned MS **of findings** that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorisation to continue the trial in accordance with **Directive 2001/20/EC**.
- ...for arranging systems and written SOPs to ensure that the necessary quality standards are observed in every step of the **case** documentation, data collection, validation, evaluation, archiving and **reporting**.

Expedited reporting of all SUSARs to all CAs within 7/15 days

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT3)

- **Seriousness:** Art 2(o) of Dir 2001/20/EC and ENTR/ CT 3 Annex 1
- **Expectedness:** Art 2(p) of Dir 2001/20/EC and ENTR/ CT3 Annex 1
– „if nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information (identified in the protocol: IB or SPC) for the IMP“
- **Causality:** Art 2(m) of Dir 2001/20/EC and ENTR/ CT3 Annex 1; frq not reported in the initial report, but required in fup reports! – unblinding (see 5.1.8 Managing adverse reactions/events in blinded trials)

5.4 Reporting of **safety issues following completion of the clinical trial** in the European Community. After termination of the CT, any unexpected safety issue that **changes the B/R analysis and is likely** to have an impact on the subjects who have participated in it, **should be reported** as soon as possible to the CAs concerned together with proposed actions.

Data Elements for Suspected Unexpected Serious Adverse Reaction (SUSAR) report

- 1. Clinical trial identification:** Clinical trial identification (EudraCT number, if applicable or the sponsor's trial protocol number)
- 2. Subject's details**
- 3. Suspected investigational medicinal product(s)**
- 4. Other treatment(s)**
- 5. Details of suspected Adverse Drug Reaction(s):**
Reaction(s) in MedDRA terminology (lowest level term)
- 6. Details on reporter of event/suspected adverse reactions**
- 7. Administrative and Sponsor details:**
... country in which reaction occurred

Primary Source / Occurrence Country - ICH E2B(R2)

A.1.1 Identification of the country of the **primary source**

User Guidance:

Data Elements for Transmission of Individual Case Safety Reports

Generally, this item would be the only country provided. Provisions have been made **to include other countries for unusual cases** concerning foreign travel and sources of manufactured material (A.1.2 and B.4.k.2.3). See the companion document for **appropriate country codes (Austria = AT)**.

A.1.2 Identification of the country where the reaction/event occurred

User Guidance:

For example, this should be the **country where the reaction was detected while the patient was traveling**, but the report was made by a health professional on the patient's return.

Beginn und Ende der SUSAR Meldeverpflichtung

Meldepflicht

Beginn: mit der Erfüllung aller Voraussetzungen für die Durchführung der Studie (i.e. positives Votum der EK und kein Einspruch durch das BASG).

Ende: mit der offiziellen Beendigung der jeweiligen Studie in Österreich.

Nebenwirkungen mit **in Verkehr gebrachten Arzneimitteln**, zugelassenen Arzneyspezialitäten und registrierten pflanzlichen Arzneyspezialitäten und deren Bestandteilen (gemäß PV-Verordnung §1)

- Spontanmeldungen
- Meldungen aus Literaturstellen,
- Meldungen aus Nicht-interventionellen Studien § 2a Abs. 3 AMG compassionate use,
- individual patient use (§ 8.(1) 2. AMG).

See <http://www.basg.at/pharmakovigilanz/sicherheitsmeldungen>

Meldungen aus **klinischen Studien (interventionell, Phase 1-4)** erfolgen an das Institut Wissenschaft & Information.

Meldungen betreffend Patienten, die in eine klinische Studie (interventionell) involviert sind, erfolgt nur dann an das Institut Pharmakovigilanz, wenn das verdächtige AM nicht Teil des Studienprotokolls/Prüfsubstanz war.

See <http://www.basg.at/en/medicines/before-authorisation/clinical-trials>

So far...

- ...we exclusively accepted SUSARs sent by fax or express letter.
 - ...international cases: CIOMS form
 - ...national cases: national SUSAR form

Bundesamt für Sicherheit im Gesundheitswesen (BASG),
Austrian Agency for Health and Food Safety (AGES) PharmMed
Institute for Science & Information (WIN)
Department for National Affairs (NATA)
Schnirchgasse 9, A-1030 Vienna, Austria
Fax: ++43 (0) 50555-36809

Since 01.01.2010...

- ... we provide the option to directly submit to EV-CTM, without written parallel reporting to BASG

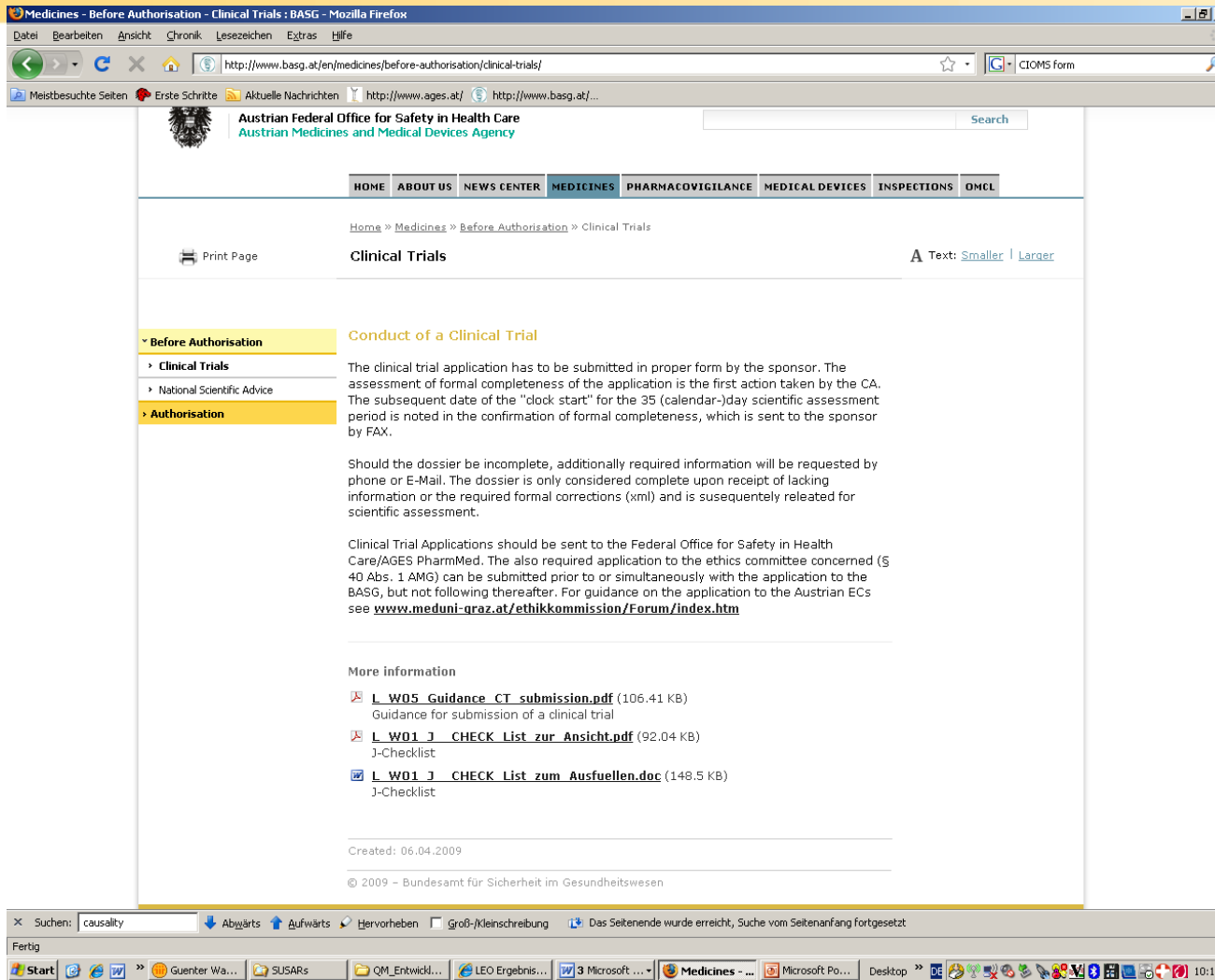
ONLY IF: a correct application has been sent to AGES PharmMed

- ...no written national SUSAR Form is required
- ... SUSARs sent by fax or express letter are still accepted

- ...link to SUSAR application form



More Infos...



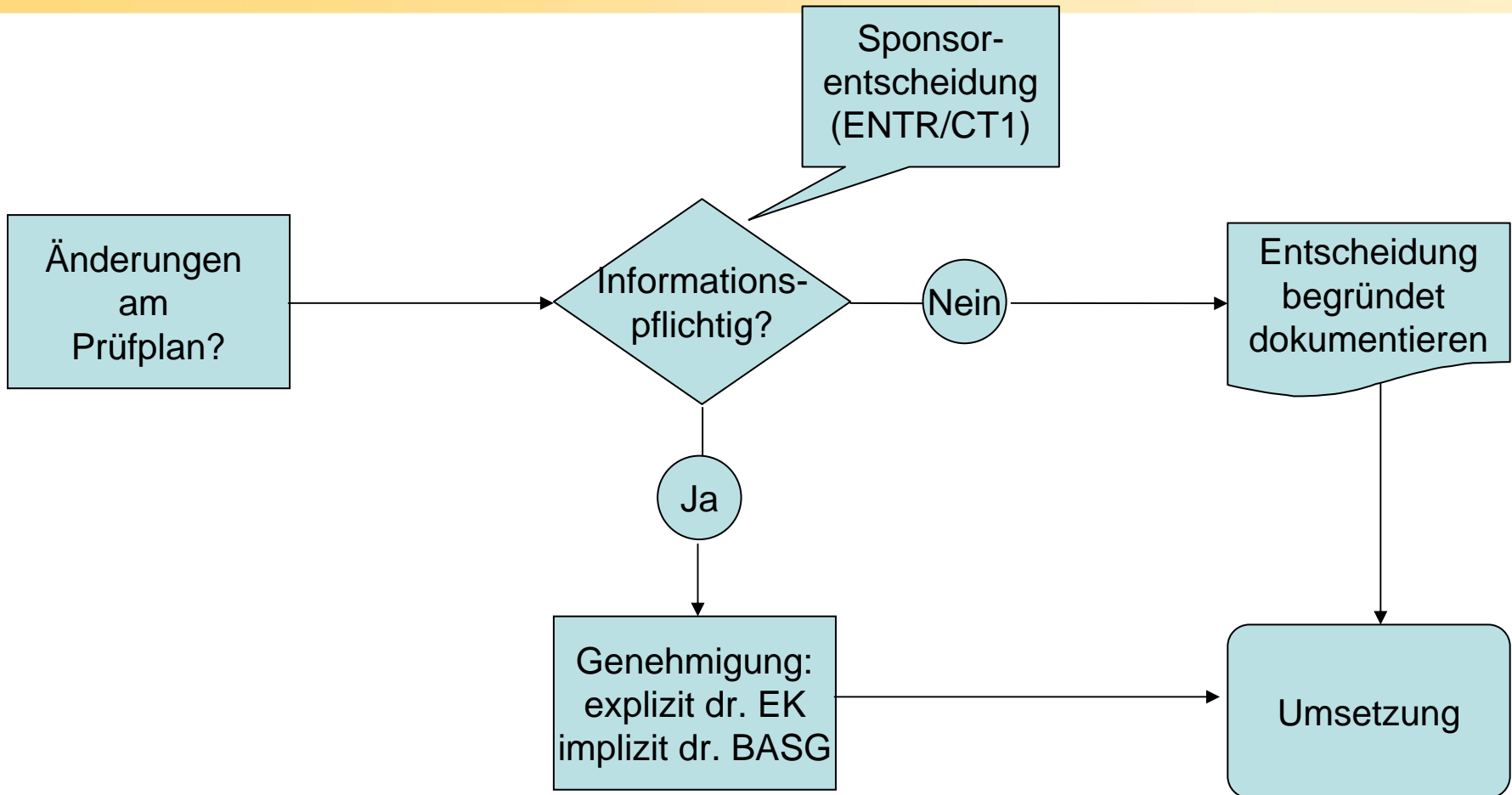
The screenshot shows a Mozilla Firefox browser window displaying the website of the Austrian Federal Office for Safety in Health Care (BASG). The page title is "Medicines - Before Authorisation - Clinical Trials : BASG - Mozilla Firefox". The address bar shows the URL: <http://www.basg.at/en/medicines/before-authorisation/clinical-trials/>. The website header includes the BASG logo and navigation tabs: HOME, ABOUT US, NEWS CENTER, MEDICINES, PHARMACOVIGILANCE, MEDICAL DEVICES, INSPECTIONS, and OMCL. The main content area is titled "Clinical Trials" and includes a "Print Page" button and a text size selector. A sidebar on the left shows a navigation menu with "Before Authorisation" expanded, containing "Clinical Trials", "National Scientific Advice", and "Authorisation". The main text discusses the "Conduct of a Clinical Trial", stating that the application must be submitted in proper form by the sponsor and that the assessment period is 35 calendar days. It also mentions that the dossier is only considered complete upon receipt of lacking information or required formal corrections. A section titled "More information" lists three PDF documents: "L_W05_Guidance_CT_submission.pdf" (106.41 KB), "L_W01_J_CHECK_List_zur_Ansicht.pdf" (92.04 KB), and "L_W01_J_CHECK_List_zum_Ausfuellen.doc" (148.5 KB). The page footer indicates it was created on 06.04.2009 and is copyrighted by the Bundesamt für Sicherheit im Gesundheitswesen in 2009. The browser's search bar at the bottom contains the text "causality".

<http://www.basg.at/en/medicines/before-authorisation/clinical-trials>

Amendments

Life changes.
When it stops
you are dead.

Flow Chart Amendments



Adaptiert nach Schriever, Bundesgesundheitsbl 2009.52:377-386
Art 10a Dir 2001/20/EC sowie AMG § 37a.

- Amendments need approval if they are 'substantial'.
- **Decision** on significance of amendments **made by sponsor**;
- Standardised Application Form
- **35 days** after submission, a substantial amendment can be considered approved if no formal response from CA
- **Suspension** of trial approval **possible**, but sponsor needs to be informed first and get an opportunity to explain and correct problems. CA needs to inform all other CAs involved in trial
- **Non-substantial**: no approval, just documented at the sponsor and at the site, ASR;

“Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial-October 2005” (ENTR/F2/BL D(2003) CT 1 Revision 2).

AMDs regarded as „substantial“ ...

...where they are likely to have a significant impact on

- safety or physical or mental integrity of subjects
 - scientific value of trial
 - conduct or management of trial
 - quality or safety of any IMP used in trial
- otherwise significant („other aspect of a trial“)

and require approval of CA and / or EC

AMDs related to the protocol (examples)

- Purpose of trial
- Design of trial
- Informed consent
- Measures of efficacy
- Schedule of samples
- Addition or deletion of measures
- Number of participants
- Age range of participants
- Inclusion or exclusion criteria
- Safety monitoring
- Duration of exposure or Change of posology of IMP
- Change of comparator
- Statistical analysis

ENTR/CT1: Attachment 5: Examples for Substantial Amendments

AMDs related to the CT arrangements (examples)

Change of

- Principal Investigator or addition of new ones
- Change of co-ordinating investigators
- trial site or addition of new ones
- sponsor or legal representative
- CRO assigned significant tasks
- definition of end-of-trial
- In the documentation used for recording study data (CRF)

ENTR/CT1: Attachment 5: Examples for Substantial Amendments

AMDs related to the IMP (examples)

- Change of name or code of IMP
- Immediate packaging material
- Manufacturer(s) or MF process of AS or product
- Specifications of active substance or product
- Specification of excipients where these may affect product performance
- Shelf-life including after first opening and reconstitution
- Major change to the formulation
- Storage conditions
- Test procedure of active substance, product or non-pharmacopoeal excipients

ENTR/CT1: Attachment 5: Examples for Substantial Amendments
Guideline on the requirements to the chemical and pharmaceutical quality
documentation concerning IMPs in CTs (CHMP/QWP/ 185401/2004 final)

Changes to non-clinical pharmac. and toxicology

...data where this is relevant to the ongoing trials
(i.e. altered risk-benefit assessment)

(examples):

Results of new pharmacology or toxicology tests

New interpretation of existing pharmacology or
toxicology tests

Results of new interaction studies

Changes to CT and human experience data

where this is relevant to ongoing trials (i.e. altered risk-benefit assessment) (examples)

Safety related to CTs or other experience with IMP in man
New data or new interpretation of existing data from

- clinical pharmacology tests
- clinical trials
- other experience in man

Note: Annual updates (ASRs, IB) are not necessarily substantial; ASRs may trigger Subst AMDs, IB update might be a subst. AMD

ENTR/CT1: Attachment 5: Examples for Substantial Amendments

Finally...

- **A TYPE OF NOTIFICATION**

A.1 Member State in which the substantial amendment is being submitted:

A.2 Notification for authorisation to the competent authority:

A.3 Notification for an opinion to the ethics committee:

A.4 Notification for information only¹:

A.4.1 To the competent authority

A.4.2 To the Ethics committee

¹ For substantial amendments to information that only the CA has previously assessed (e.g. quality data in most of the MS), the sponsor should not only submit the amendment to the CA but also inform the ethics committee that they have made the notification indicating that it is “for information only”. Similarly, the sponsor should inform the CA of any notification of a substantial amendment to information which was previously only assessed by the ethics committee (e.g. facilities for the trial).

- **don't forget the xml!**



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Questions ?

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www.ages.at