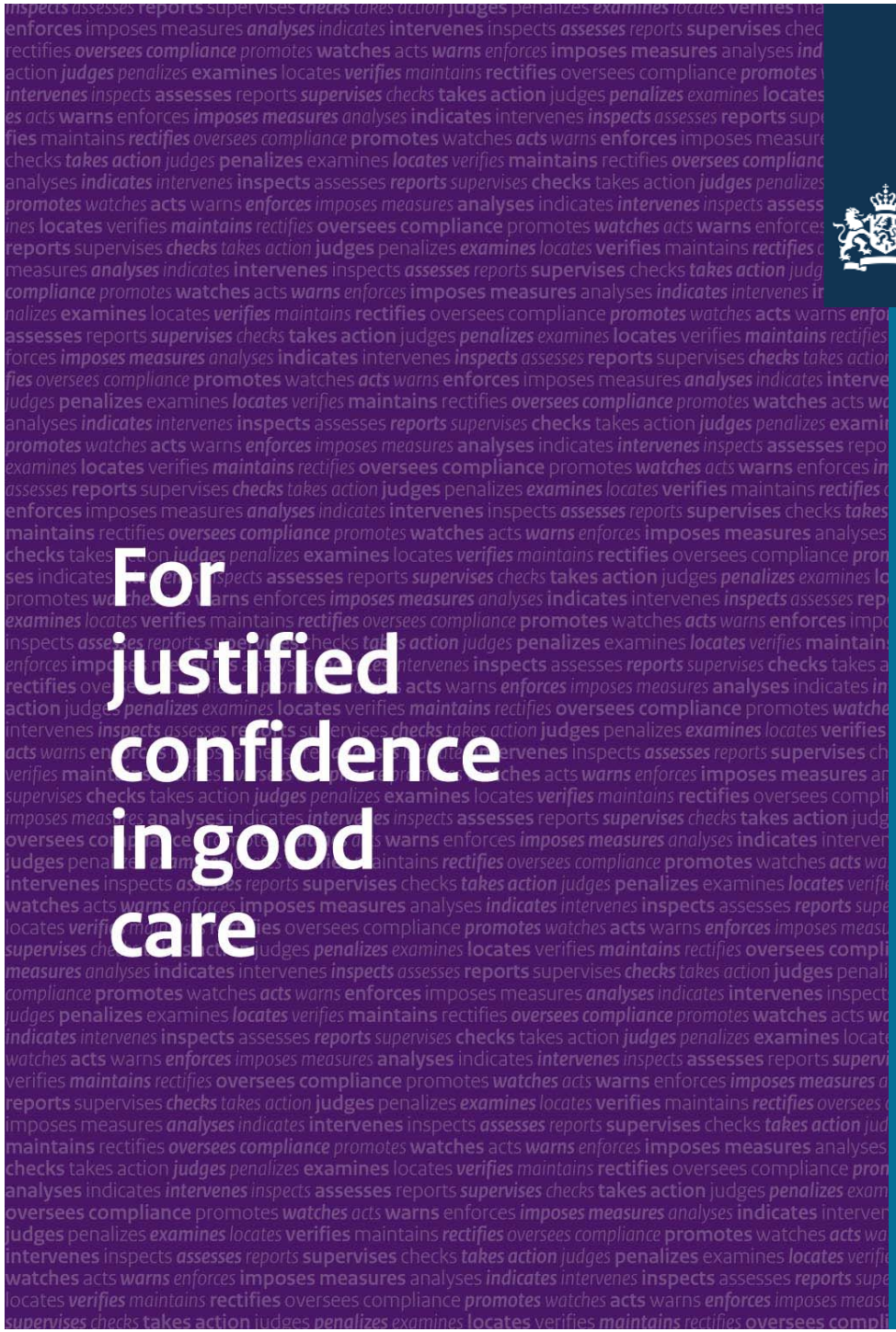


Health Care Inspectorate
Ministry of Health, Welfare and Sport

Good Clinical Practices (GCP) in developing settings: The promotion of the international harmonization for the respect of ethical principles, human rights and justice

On behalf of the Clinical Trials Unit

of the

Health Care Inspectorate,
The Netherlands

Presenter: Dr. Willem R. Verweij
Senior Inspector (for Clinical Trials)

11 – 14 June- 2012, Mwanza

For justified confidence in good care

Health Care Inspectorate
Ministry of Health, Welfare and Sport

The 5 W's

- WHO
- WHAT
- WHERE
- WHEN
- WHY

14 June 2012, GCP in developing settings, Mwanza

Health Care Inspectorate The Netherlands

Health Care Inspectorate
Ministry of Health, Welfare
and Sport (Dutch: VWS)

4 regional offices:
- The Hague *(Prog. 8* + 'Rijswijk'*)*
- Amsterdam
- Zwolle
- 's Hertogenbosch

1 Knowledge and Training Centre:
- Utrecht

IGZ (Health Care Inspectorate)

The Netherlands Health Care Inspectorate *(IGZ))*

≈ 490 employees

10 programs (8 – Pharmaceutical Products and Medical Technology)

Program 8 consists of:

- GMP/GDP
- GCP (**5** + 1 Inspectors)*
- PhV (2 + 2 Inspectors)*
- Blood and Tissues
- Opiates
- Marketing and Promotion of Medicines ('advertisement' for marketed medicinal products is not allowed in The Netherlands)

* + supporting assistance (Program Officer (1 GCP, 1 PhV))

The perspective / ‘disclaimer’

This presentation, coming from a Dutch inspector, will reflect the international (ICH-GCP), European and partly national perspective, definitions, requirements and authority/ jurisdiction, focus on studies with and MAA for medicinal products and keeping in mind :

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA ……..

Be aware of additional (inter-)national or continental legislation and regulations.

Note:

Within the regions for which the ICH-GCP Guideline is used as a unified standard to facilitate the mutual acceptance of clinical data by the regulatory authorities, differences do exist as to the legal status of and/or reference to this Guideline.

Some things beforehand

Different kind of Marketing Authorisation Application (MAA) Dossiers:

- Centralised (➔ for all EU MS's + EEA) ➔EMA

But also:
- Decentralised (DCP)
- Mutual Recognition (MRP)
- National

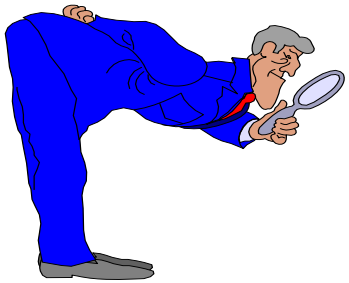
and of course many studies not (directly) related to MAA.

This presentation focuses on Centralised Procedures and:

EMA no inspectors 'herself' (i.c.t. FDA) ➔ 'ALL' EU-GCP inspectors

WHO ? (not being the World Health Organisation)

Definitions, international and national legislation + regulations



The Inspector / Inspection team

ICH-GCP: NO real definition (but definition of: Inspection)

EU-level: EC Directive 2005/28: Qualifications of inspectors

National level: National Legislation

WHO (cont'd)

Definition of Inspection:

The act by a **regulatory authority(ies)** of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the **regulatory authority(ies)**. (ICH-GCP 1.29)

SO

You represent/are the regulatory authority(ies) ➔

- Rights
- Responsibilities
- Requirements

It’s a great job, but for sure: “not just a job for everyone”

Requirements / Qualifications

- ICH-GCP	None explicitly
- EU-level	2005/28/EC (Directive ➔ implemented in national legislation)
- National level	Any national law, Additional training, qualifications, categories (senior, specialist, expert)

Bottom line: Appropriate education, training, knowledge, experience, procedures, well documented.

Inspection Team

- Tailor made: Choose from education, experience, interest, availability, (legal) need/requirement (also: training, observer)
  ➔ MADE TO MEASURE

- Well-prepared: ➔ CSR, Protocol, Patient Listings, Assessor, Experts, (inter-) national colleagues, etc.

- Additional persons: Translator/Interpreter, Assessor, (national) observer(s)

- (Fit, Enthusiast and Focused)

WHAT ?

Definitions, international and national legislation + regulations

The Inspection

ICH-GCP:	Again: ICH-GCP 1.29
EU-level:	EC Directive 2001/20: Inspection
National level:	Additional rights and/or restrictions

WHAT (cont'd)

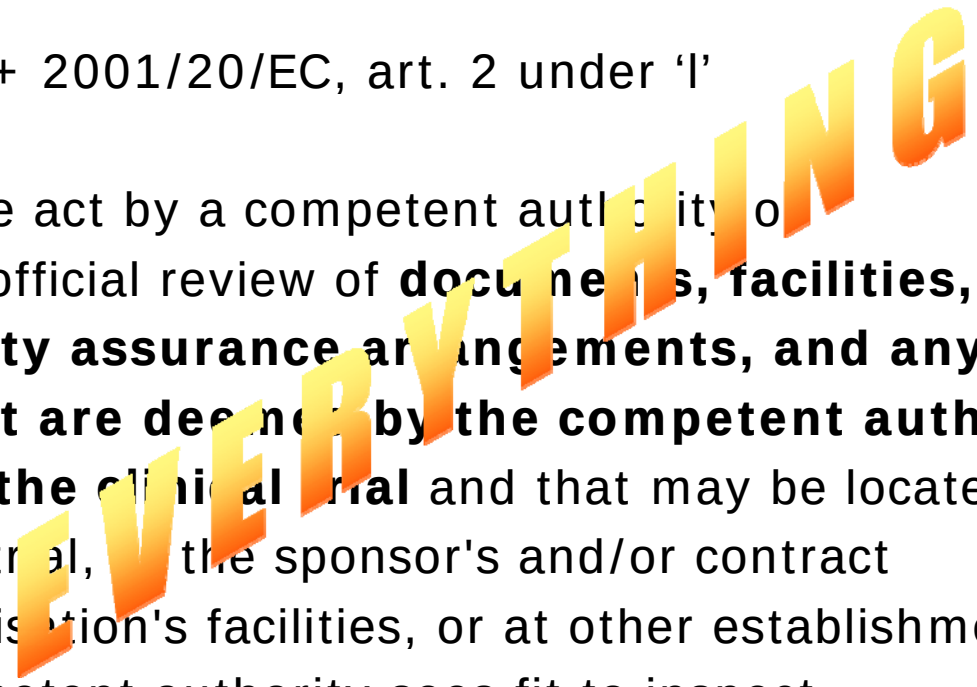
ICH-GCP 1.29 + 2001/20/EC, art. 2 under 'l'

'inspection': the act by a competent authority of conducting an official review of **documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial** and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect

WHAT (cont'd)

ICH-GCP 1.29 + 2001/20/EC, art. 2 under 'l'

'inspection': the act by a competent authority of conducting an official review of **documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial** and that may be located at the site of the trial, or the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect



WHAT (cont'd) Inspection Conduct

Inspection practices:

- Inspect (Review+Verify), Interview, Access, Testing, Evaluation

Aim:

- Evaluate the quality and correctness (➔ reliability) of the data and systems implemented and ensure the safety and well-being of the subjects in the clinical trial is/was respected

Inspection strategy:

- Follow the process ('rebuild the study')

WHAT (cont'd): Preparation by site

What needs to be available

- Documentation
- Study (related) facilities / 'Environment'
- Access

Who needs to be available

- Responsible (= Key-) Persons (e.g. PI, sub/co invest, SN, monitor, but could also: representative(s)EC, Board of Directors, etc.

How to prepare

- Communication
- Personnel
- Documentation

WHERE ?

ICH-GCP 1.29 + 2001/20/EC, art. 2 under ‘l’

‘inspection’: the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be **located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect**

WHERE ?

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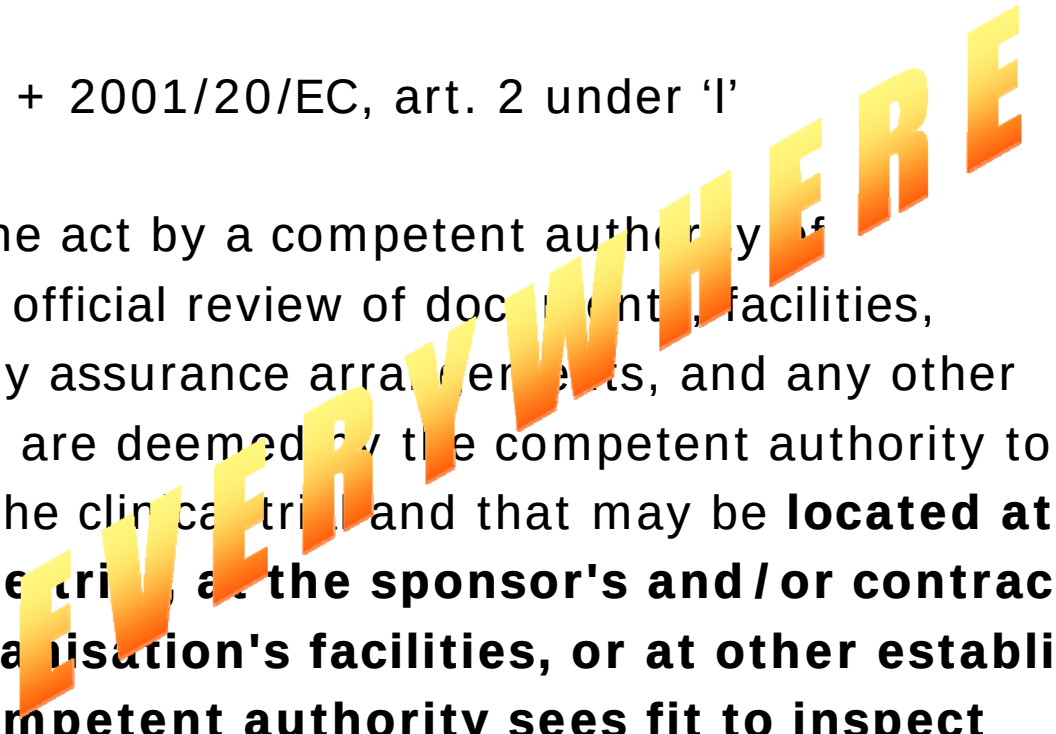


WHERE cont'd

- Sponsor, CRO (various types)
- Investigator
- Pharmacy
- Laboratory, Specialised departments
- Manufacturer, Vendor, Archives
- Sub-contractors
- Ethics Committee / Review Board ((M)EC/MRC or IRB)

.....

WHERE cont'd

- Sponsor, CRO (various types)
- Investigator
- Pharmacy
- Laboratory, Specialised departments
- Manufacturer, Vendor, Archives
- Sub-contractors
- Ethics Committee (MEC/MRC or IRB)

EVERYWHERE

WHEN ?

Two main, obvious choices:

- **During** the conduct of the study

- **Post** conduct (sometimes LONG post conduct; i.e. in case of an MAA. Most extreme: study that started in 1993 lasting until 2003, inspected in 2007 ➔ oldest data 14 (!) years and ‘ before ICH-GCP’

-(**PRE**: in case of specialised sites (e.g. phase I))

WHEN cont'd: **During**, Pro's and Con's

PRO's:

- Real life, no / not only paper reality

- Corrective (and preventive) actions can be implemented 'right away' ➔
  e.g. subject safety

- Nothing like: ' archived away' / not easily accessible, key-personnel no longer available, " I don't remember" / " so long ago"

- ..... (e.g. public perception)

WHEN cont'd: **During**, Pro's and Con's

CON's:

- Study not completed ➔ some/many procedures, steps, analyses, follow-up, etc. not (yet) done

- No complete overview

- Site / people might feel 'of the hook'

WHEN cont'd: **Post**, Pro's and Con's

..... the previous slides 'visa – versa'

WHY ?

Purpose:

- Verification of safety of subject and quality of trial and trial data and of GCP (➔ VERIFY GCP-compliance (next slide))

Thus:

- **Every** trial (notified/submitted to EC) is, in principle, a candidate for an inspection

But:

- Cost/effectiveness/resources of inspections

Therefore:

- Decision criteria needed for when/why/how inspection is the most optimal tool and most optimally used

What is GCP Compliance

ICH-GCP definition of compliance:

- *Adherence to **ALL** the trial related requirements, Good Clinical Practice (GCP) requirements and the applicable regulatory requirements.*

WHY ? cont'd

Two main reasons:

- **TRIGGERED**

- **non-TRIGGERED / ROUTINE** / own initiative

WHY cont'd

TRIGGERED:

- Signals during conduct (subjects, SAE's, EC's, PI / sub invest., other MD's, etc.)

- Signals during assesment of CSR (MAA) + response to LoQ

- Other Signals (Merges, Bankruptcy, etc.)

WHY cont'd

Signals / Triggers are 'never' absolute ➔
Papers of triggers (e.g. BE from GCP/CMD subgroup)

Based on their:

- severity (complaints ..... FRAUD)
- origin (subject ..... PI ..... dissatisfied employee)
- number (single ➔ multiple)
- (politic)
- .....

Careful evaluation (+ contact) ➔ decision process / SOP
+ good communication with assessors (+ EC's)

WHY cont'd

non-TRIGGERED / ROUTINE / own initiative

- National program

- Legal obligation (e.g. GMP Manufacturing sites every 3 years)

- Thematic Inspections (e.g. Minors, Elderly, Unable to give Informed Consent (stroke), Phase I, CRO's, Investigator Initiated Trial, etc.)

- New site / Unknown Sites (could be a 'trigger')

- ……

SO :

…… a Tailor-made team

…… well educated and prepared

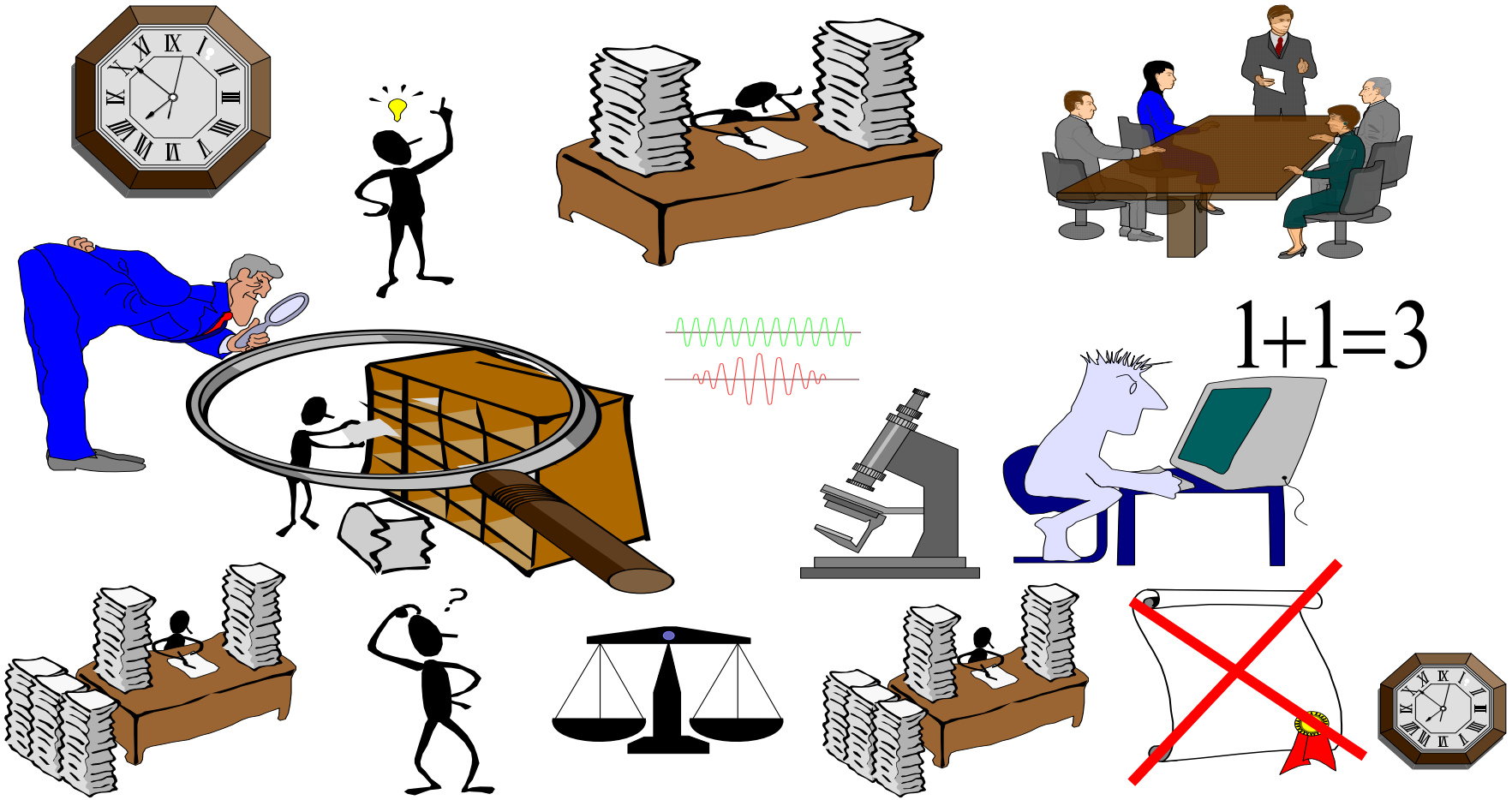
…… verifying patient safety, data integrity and GCP-compliance

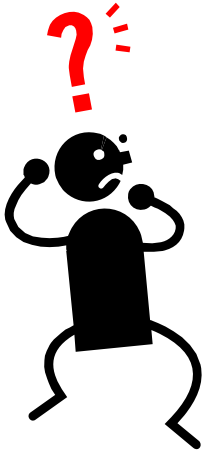
…… going ‘everywhere’ study related

…… inspecting (before,) during or after study conduct

…… because of legal requirement, needs, general safety

GCP Inspection Procedures







QUESTIONS



Thank you for your attention

On behalf of The Clinical Trials Unit
of the Health Care Inspectorate
The Netherlands

Questions or further information:

Dr. W.R. Verweij (wr.verweij@igz.nl)

or put your questions to
gcp@igz.nl

(Or, of course, the organising committee)