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Ensuring GCP Compliance in Investigator Initiated Trials (IITs)- A Case Study

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Outline

- Introduction: why need to ensure GCP compliance?

- How to ensure GCP compliance in IITs?
  - ✓ Practical steps
  - ✓ A case study: how PI, CRC and study team work together to address/resolve challenges encountered during the study conduct and ensure GCP compliance

- Conclusions

Why Need to Ensure GCP Compliance?

- Provide public assurance that the rights, safety and well-being of trial subjects are protected, and that the clinical trial data are credible (ICH-GCP E6 (R2), 2016, page 1).

- Singapore regulatory requirements.

Medicines (Clinical Trials) Regulations

Duty to comply with guidelines and instructions of licensing authority

21. Every sponsor, principal investigator or holder of a certificate shall comply with any guidelines or instructions relating to the conduct of clinical trials issued by the licensing authority and notified to such sponsor, principal investigator or holder of a certificate, including the Singapore Guideline for Good Clinical Practice.

How to Ensure GCP Compliance in IITs?

PI, CRCs and the study team need to be well versed with the GCP guidelines

The Sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials

(ICH-GCP, monitoring 5.18, page 29)

In addition, from PI and CRC's perspective, some practical steps are also useful to ensure GCP compliance in running an IIT.

8 Practical Steps

From both PI and CRC's perspective

- ✓ Proper planning of the study and adequate training of the study team.
- ✓ Involve CRC early in the design of study workflow.
- ✓ Develop Standard Operating Procedures (SOPs) to ensure standardization of study procedures.
- ✓ Understand the need for monitoring and implement necessary actions to rectify monitoring findings. .
- ✓ PI is the leader and must take charge of the research study.
- ✓ Documentation is important.
- ✓ Effective communication among the team.
- ✓ Maintain good working relationships with various stakeholders

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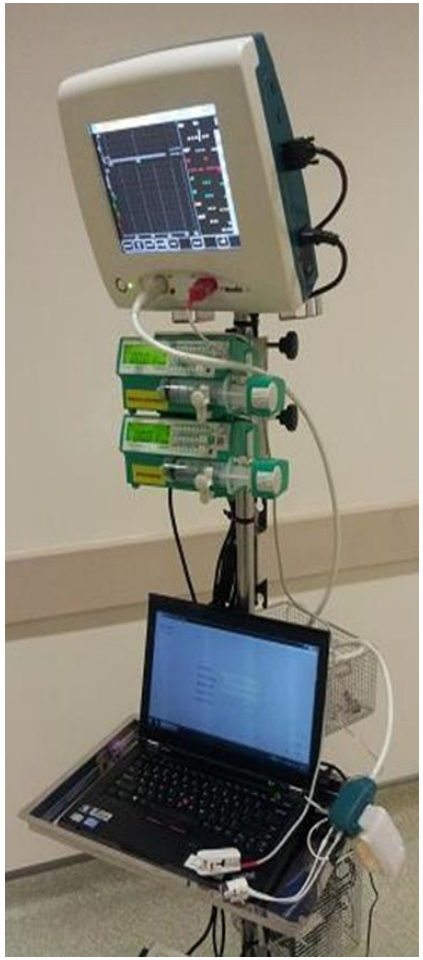
An IIT: DIVA Study

- **Project title:**
  - *A novel closed-loop DIVA system for the maintenance of haemodynamic stability to improve perioperative outcome during spinal anaesthesia for caesarean section*
  - ***DIVA: Double intravenous vasopressor automated***
  - ***Vasopressors** used included phenylephrine and ephedrine*

- **Primary hypothesis:**
  - to investigate the experiment group using DIVA compared to the control group using manual boluses in terms of the ***incidence of hypotension***, defined as SBP<80% baseline

- **Overall aim:**
  - to ***develop DIVA system***, integrated by a unique clinical algorithm for vasopressor delivery to allow a greater ***control of patients' hemodynamic status*** during spinal anaesthesia for Caesarean section.



Study Background

Study PI & CRC	A/P Sng Ban Leong & CRCs from KKRC
Approval	CIRB & HSA
Study period	01 Jun 13 – 28 Oct 15 (Last patient Last Visit)
Recruitment No.	296
Research Location	Women's Operating Theatres
Current Status	Data analysis, manuscript revision
Monitoring	Conducted by SingHealth Research Compliance Management (RCM) Unit

1. Proper Planning and Adequate Training

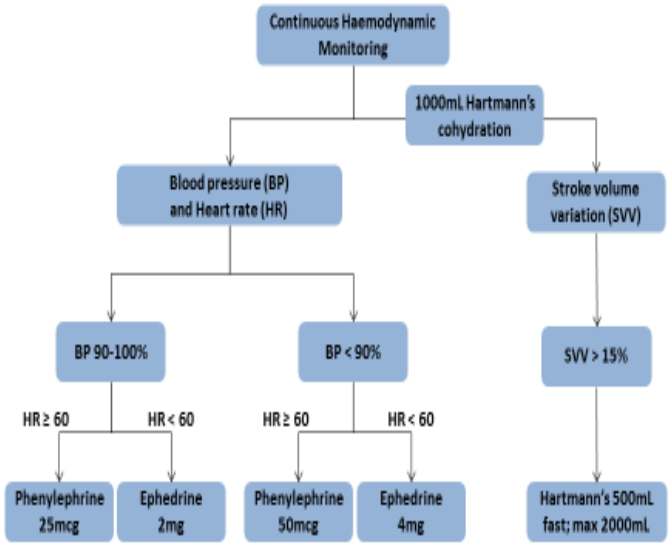
- Getting approvals from ethics committee and regulatory authorities
  - IRB and HSA

- Site Initiation Visit
  - To be conducted prior to the commencement of study
  - Involves protocol training for study team members. Such as Co-investigators, CRCs, OT nurse managers, OT staff nurses, etc.

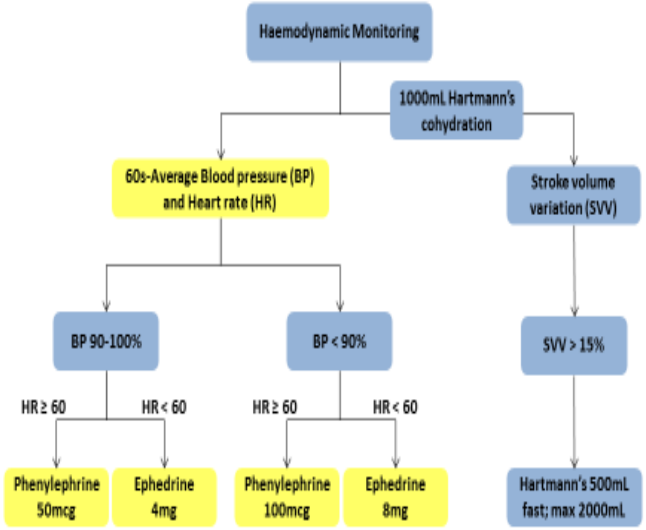
1. Proper Planning and Adequate Training

Systematic trainings were conducted for the study team to ensure every team member knows his/her respective roles and responsibilities.

Dosing algorithm (experiment group)



Control group dosing algorithm



2. Involve CRC Early

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Key Roles & responsibilities of CRCs	
1	CRCs play a key role in the implementation of IITs, and a significant role in the success of the research study.
2	CRCs perform multiple tasks during the conduct of research with different skill sets. Such as assist in informed consent taking process, study workflow design, subject recruitment, adverse event reporting, data collection and entry, etc.
3	Play a critical role in ensuring IITs are conducted in accordance to the protocol, **GCP** & applicable regulatory requirements.

(Reference from Rico-Villademoros, et al. 2004)

3. Develop SOPs

- Include specific instructions in the written documents to ensure standardization of study procedures, maintain consistency and ensure GCP compliance.

- For DIVA study, the team seek advice on IP management SOP from SingHealth RCM unit.

4. Understand the Need for Monitoring

RCM Monitoring

- Monitoring is not fault finding
- Help the study team to identify gaps and work together to rectify them.
- Initial monitoring →12-14 Nov 2013
- Total of 2 monitoring visits
- 4 offsite monitoring visits

4. Understand the Need for Monitoring

Monitoring Findings (1)

Issue: Temperature monitoring log for Investigational product (IP) (Ephedrine and Phenylephrine) involved in study is not applicable.

4. Understand the Need for Monitoring

Requirements

- IP Temperature Monitoring
  - In drug trials, sites are required to monitor temperature of IP, as according to Health Science Authority (HSA) guidelines on IP management:

"3.1.1. Thus, the investigator should ensure that the IP is stored in an area where the access is secure and limited; and maintain IP Storage Temperature Records."

(Reference: HSA Clinical Trials Guidance: Alternative Measures for Investigational Product Management for Clinical Trials of Locally Registered Therapeutic Products or Medicinal Products.)

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4. Understand the Need for Monitoring

Requirements

- *3.2. Alternative Measures for IP Storage*
  - *3.2.1. Separate IP Storage Temperature Records may not be required if the existing hospital pharmacy system for temperature monitoring is utilized. It would be recommended to ensure that the temperature monitoring system is calibrated and maintained regularly; an alarm system is available for temperature excursions; and a copy of the temperature monitoring records is filed in the Investigator Site File.*
  - *3.2.2. If the hospital pharmacy does not monitor the storage temperature of medicinal products stored at ambient temperatures, it would be recommended that an alarm system should be available to detect temperature excursions.*

(Reference: HSA Clinical Trials Guidance: Alternative Measures for Investigational Product Management for Clinical Trials of Locally Registered Therapeutic Products or Medicinal Products.)

4. Understand the Need for Monitoring

Solutions

- IP Temperature Monitoring
  - Temperature in OT is properly maintained at room temperature by KKH Facility Management according to KKH Standard of Practice
  - Therefore, study team does not need to monitor and record temperature
  - A file note was put up to explain that there is no need for the study team to maintain a IP temperature log
  - File note sent to HSA to inform them

4. Understand the Need for Monitoring

Monitoring Findings (2)

Issue: IP Preparation

- According to IP management SOP, IP Phenylephrine is pre-diluted by pharmacist

- However, there was an instance when the pre-diluted drug were run out in the OT, the IP Phenylephrine was pre-diluted by the study Co-I
  - unavoidable logistical issue due to unpredictable usage rate in the OT

4. Understand the Need for Monitoring

Corrective Actions

- IP Preparation
  - As Investigator prepared IP Phenylephrine was not written in the study protocol, non-compliance was submitted to IRB;
  - Protocol and IP SOP was revised to include workflow for investigator for pre-dilution of IP Phenylephrine;
  - Protocol and IP SOP submitted to IRB and HSA for approval.

4. Understand the Need for Monitoring

Monitoring Findings (3)

Issue: Blinding

- For trials involving blinding, HSA recommends separate blinded and unblinded CRCs, for clear delineation of responsibilities to minimize risk of accidental treatment unblinding

- But due to limited resources, there were no blinded CRCs in this study

4. Understand the Need for Monitoring

Corrective Actions

- Unblinded CRCs had to assume responsibilities to conduct blinded activities
  - Maintenance of investigator site files
  - Making sure unblinded documents (randomization) are kept from blinded study team members

5. PI is the leader

Key Roles and Responsibilities of the PI -Reference from ICH GCP E6(R2), pg13	
1	Overall responsible for the proper conduct of the clinical trial
2	Should be familiar with the investigational product management
3	Should be aware of and comply with GCP and the applicable regulatory requirements
4	Should permit monitoring and auditing by the sponsor, and inspection.
5	Responsible for supervising any individual party or party to whom the Investigator delegates study tasks conducted at the trial site

6. Documentation is Important !

- In clinical research, “What is not documented is not done!”
- Lack of reliable, accurate and adequate source documentation-one of the most common inspection findings in US-FDA investigator site inspections & the most common pitfall identified during sponsor audits (Bargaje, 2011).
- Documentation is important to ensure that the study results are built on the foundation of credible and valid data (Bargaje, 2011).
- Therefore, for DIVA study, our source documentation adopted the ALCCOA attributes.

ALCCOA

Attributable,
Legible,
Contemporaneous,
Consistent
Original
Accurate

6. Documentation is Important !

Monitoring Findings (4) & Corrective Actions

- Delegation Log
  - Signatures of some study team members on the delegation log, CVs, consent forms and other documents are not the same

- Corrective Actions:
  - RCM monitor advised that study team members include all signatures in the delegation log.

7. Effective Communication

Communicating with various stakeholders

- **Communicating with** study team members and collaborators involved, such as OT nurse managers, OT staff nurses, CRCs, vendor, etc.
- **Informing** on the initiation of study and **discussion** on study workflow

Constant Communication

- **Provide regular study updates** with study team members
- **Regular meetings** to monitor study progress
- **Seek team members' input** to come out solution to improve the workflow and quality of the study

Seeking advice from SingHealth RCM

- Working closely with SingHealth Research Compliance Management (RCM) Unit to ensure study procedures are conducted according to GCP requirements

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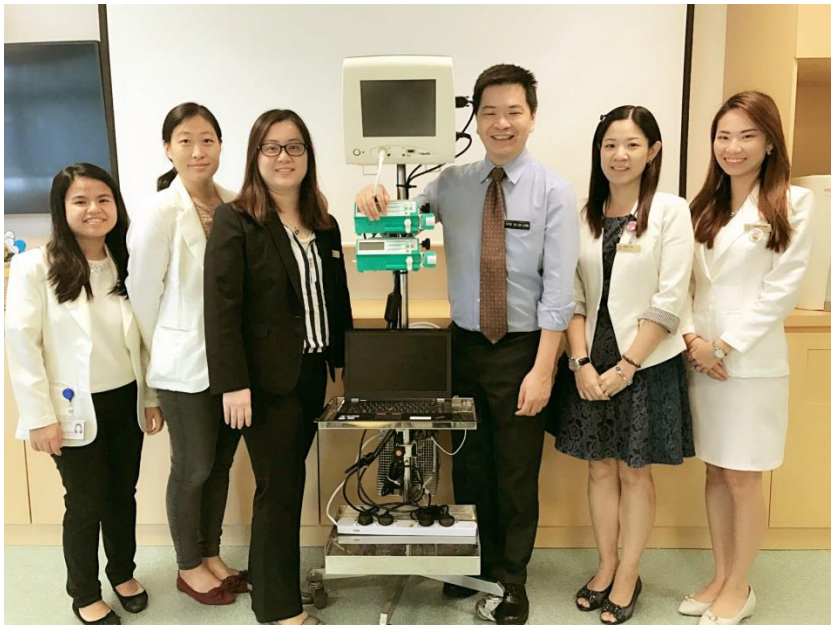
8. Maintain Good Working Relationship

Easier to ensure GCP compliance, when:

build & maintain good working relationships within the study team members, and with the clinical team.



Conclusions

To ensure GCP compliance in IITs,

- the sponsor/PI should implement a system to manage quality throughout the study.

- Good documentation and communication are the two keys.

THE TAKE-HOME MESSAGE

CRCs should define the improvements or issues needed to resolve, open disclosure to PI and team, making definite **practical steps** to close the gap and notification to research compliance agencies.

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References

Bargaje, C. (2011). Good documentation practice in clinical research. Perspectives in Clinical Research, 2(2), 59–63. http://doi.org/10.4103/2229-3485.80368

HSA Clinical Trials Guidance (2017). Alternative Measures for Investigational Product Management for Clinical Trials of Locally Registered Therapeutic Products or Medicinal Products. Available at: http://www.hsa.gov.sg/content/dam/HSA/HPRG/Clinical_Trials/Guidance/HSA_CTB_Guidance_Alternative_Measures_for_IP_Management_2May2017.pdf

International Conference for Harmonization Guideline for Good Clinical Practice (ICH-GCP E6 (R2), 2016.

Medicine Act (1978), Medicines (Clinical Trials) Regulations. Available at: http://statutes.agc.gov.sg/aol/search/display/view.w3p;ident=7e3c748b-8089-4699-a4b2-9f66af6f7820;page=0;query=Id%3A%2277f5cd55-c86e-485b-b7c9-846626e4fc1a%22%20Status%3Ainforce%20ValidTime%3A20141007000000%20TransactionTime%3A20141007000000;rec=0#legis

Rico-Villademoros, F., Hernando, T., Sanz, J.-L., López-Alonso, A., Salamanca, O., Camps, C., & Rosell, R. (2004). The role of the clinical research coordinator – data manager – in oncology clinical trials. BMC Medical Research Methodology, 4, 6. http://doi.org/10.1186/1471-2288-4-6

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