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Quality Assurance in Clinical Research

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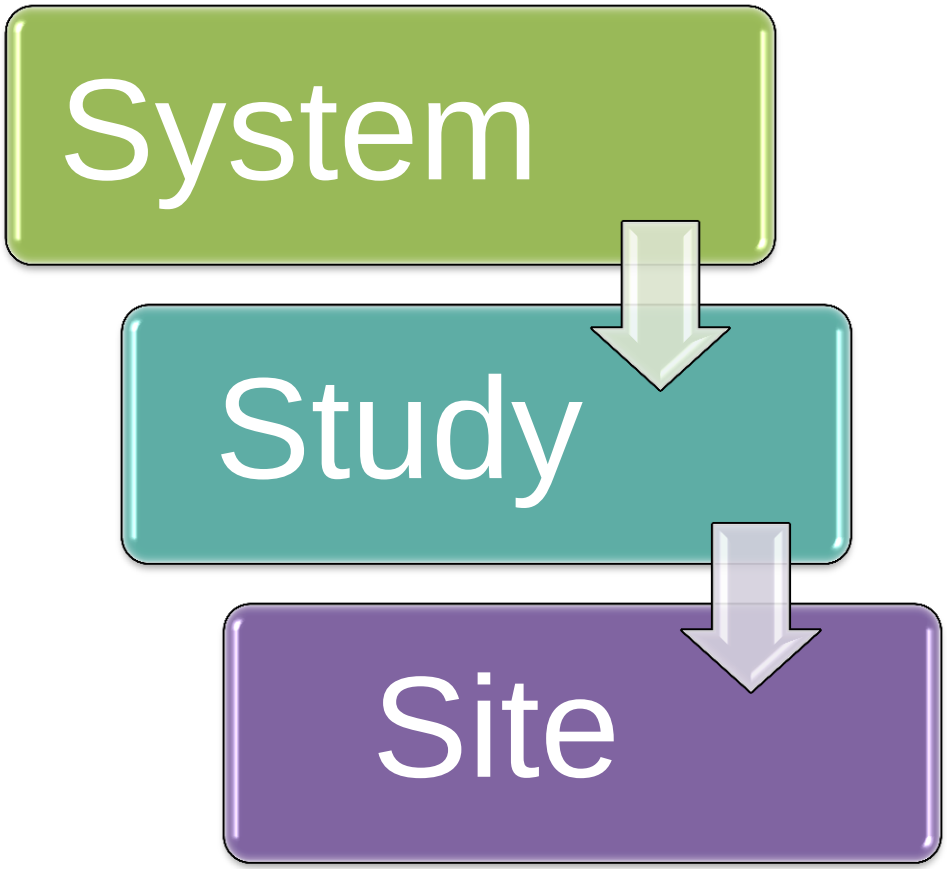
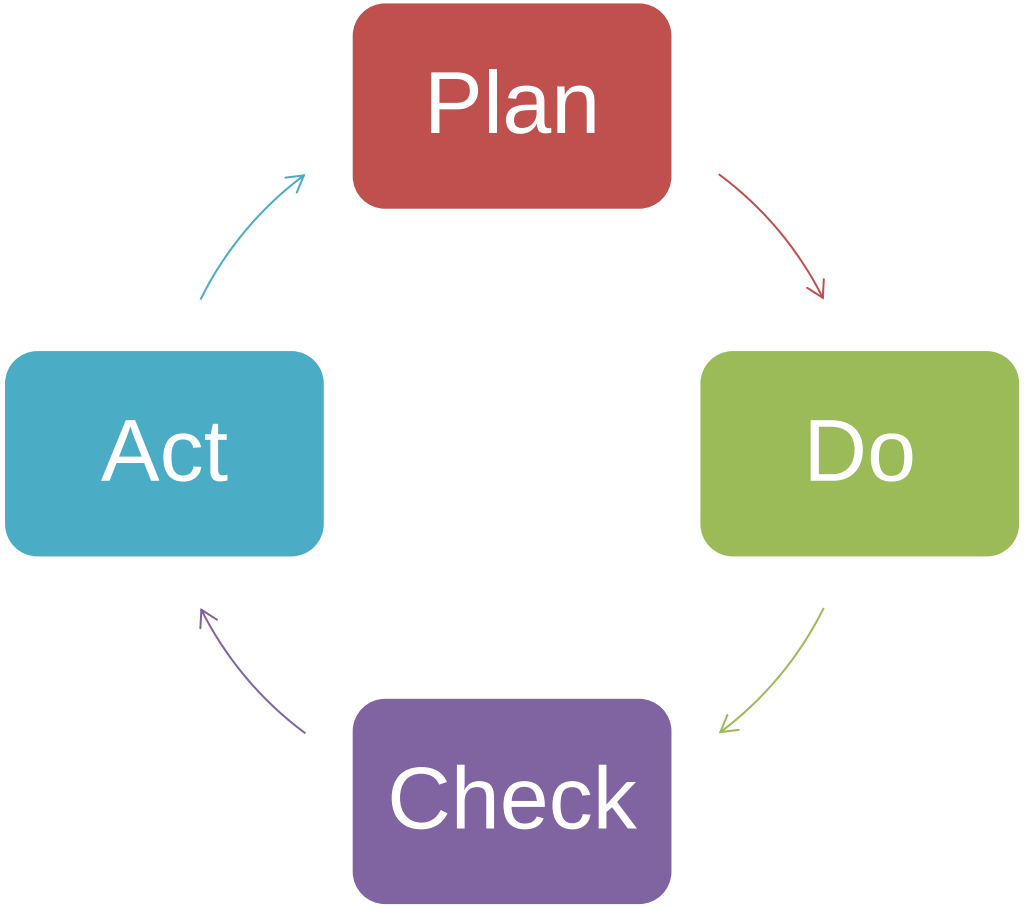
SYSTEMS & STANDARDS OF QUALITY


System
Study
Site


Plan
Do
Check
Act

What is Quality Assurance (QA)?

- A program for the systematic monitoring and evaluation of the various aspects of a project, service, or facility to ensure standards of quality are met

Standards of Quality

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Good Clinical Practice guidelines (ICH GCP)
2. Food and Drug Regulations (Division 5)
3. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2)
4. Study protocol
5. Institutional policies

ICH GCP

- Developed in 1990 by representatives of the regulatory agencies of the European Community (now the EU), Japan and the US
- An international standard for designing, conducting, recording and reporting trials that involve the participation of human subjects
- Compliance provides public assurance that the rights, safety and well-being of trial subjects are protected
- Describes the responsibilities of all participants in the conduct of clinical trials
    - Investigators, monitors, sponsors, IRBs (REBs)

Health Canada
Food & Drug Regulations

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Division 5 – Drugs For Clinical Trials Involving Human Subjects

- C.05.001 – Interpretation
- C.05.002 – Application
- C.05.003 – Prohibition
- C.05.004 – General
- C.05.005 – Application for Authorization
- C.05.006 – Authorization
- C.05.007 – Notification
- C.05.008 – Amendment
- C.05.009 – Additional Information and Samples
- **C.05.010 – Sponsor's Obligations – Good Clinical Practice**
- **C.05.011 – Sponsor's Obligations – Labelling**
- **C.05.012 – Sponsor's Obligations – Records**
- **C.05.013 – Sponsor's Obligations – Submission of Information and Samples**
- **C.05.014 – Sponsor's Obligations – Serious Unexpected Adverse Drug Reaction Reporting**
- **C.05.015 – Sponsor's Obligations – Discontinuance of a Clinical Trial**
- C.05.016 – Suspension and Cancellation

Tri-Council Policy Statement: Ethical Conduct for Research Involving Human Participants (TCPS 2)

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- Joint policy of Canada's top 3 federal research agencies
  - Canadian Institutes of Health Research (CIHR)
  - Social Sciences and Humanities Research Council of Canada (SSHRC)
  - Natural Sciences and Engineering Research Council of Canada (NSERC)
- Researchers and institutions must comply with the policy in order to hold these funds
- TCPS2 covers ethical domains of research conduct:
  - Consent, fairness, privacy, ethics review, conflict of interest, etc.

Protocol & Policies

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Study Protocol

- Quality Control and Quality Assurance are generally required sections required by GCP (section 6.11)
- "Quality by Design"

Institutional Policies/Procedures

- 024-RSJ-H Research Training Requirement (ICH GCP, HC-D5, TCPS2)
- 007-RSJ-H Research Involving Humans
- 033-RSJ-H Internal Clinical Study Audit
- Network-of-Networks (N2) Standard Operating Procedures (SOPs)

N2 SOPs

- Developed through the collaboration of all N2 member organizations in an effort to standardize clinical research operations across Canada
- Adopted by SJHH, HHS and McMaster in 2010
- SOPs are developed in compliance with HC regulations, ICH GCP, and TCPS2
- Updated every few years, the latest version being released May 15, 2015
- Available on the MyStJoes intranet site

SOP# version	Title	Effective Date (dd-Mon-yyyy)
N2 SOPs (001 – 019, 023 - 025)		
001_06	Standard Operating Procedure (SOP) Administrative Management by Network of Networks	15-May-2015
002_06	Research Team Roles and Responsibilities	15-May-2015
003_06	Research Team Training	15-May-2015
004_06	Clinical Research Protocol Feasibility and Site Selection	15-May-2015
005_06	Study Initiation/Activation	15-May-2015
006_06	Informed Consent Forms	15-May-2015
007_06	Research Ethics Board: Submissions and Ongoing Communication	15-May-2015
008_06	Informed Consent Process	15-May-2015
009_06	Subject Recruitment and Screening	15-May-2015
010_06	Management of Investigational Products	15-May-2015
011_06	Management of Biological Specimens	15-May-2015
012_06	Serious Adverse Drug Reaction Reporting in Clinical Trials	15-May-2015
013_06	Study Monitoring and Communication	15-May-2015
014_06	Clinical Data Management	15-May-2015
015_06	Investigator Study Files and Essential Documents	15-May-2015
016_06	Study Close-Out	15-May-2015
017_06	Audits and Inspections	15-May-2015
018_06	Clinical Trial Application (Drugs)	15-May-2015
019_06	Confidentiality and Privacy	15-May-2015
020_01	*CRF Design; this SOP was re-numbered to 100_02 in May 2011*	
021_01	*Study Analysis and Reporting; this SOP was re-numbered to 101_02 in May 2011*	
022_01	*Protocol Development; this SOP was re-numbered to 102_02 in May 2011*	
023_02	Clinical Trial Application (Natural Health Products)	15-May-2015

SOP# version	Title	Effective Date (dd-Mon-yyyy)
024_02	Investigational Testing Authorization (ITA) for Medical Devices (non-IVDD) and Manufacturer/Sponsor Obligations	15-May-2015
025_02	Equipment Calibration and Maintenance	15-May-2015

SOP# version	Title	Effective Date (dd-Mon-yyyy)
Investigator-Initiated (IIS) SOPs (100 -109)		
100_04	CRF Design	15-May-2015
101_04	Study Analysis and Reporting	15-May-2015
102_04	Protocol Development	15-May-2015
103_03	Data Management Plan	15-May-2015
104_03	Database Set-up	15-May-2015
105_03	Database Maintenance and Management	15-May-2015
106_03	File Transfer	15-May-2015
107_03	Database Lock and Archiving	15-May-2015
108_03	System Set-up, Maintenance and Security	15-May-2015
109_03	System Backup and Recovery Planning	15-May-2015

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Audit & Inspection Procedures

Who Does What?

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Conducted By:	Terminology
Regulatory Agency (HC, FDA, EMA)	Inspection
Third party (independent of and separate from routine monitoring or QC functions)	Audit
Internal	Monitoring

The Steps

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1. Selection/Initiation
2. Pre-Inspection Meeting
3. Review
    - Regulatory Binder
    - Patient Files
    - Facilities
4. Close-out Meeting
5. Report
6. Follow-up

Selection/Initiation

A study is selected for review by:

- Volunteered by the investigator
- Random selection
- The practice of “risk-based monitoring”

Risk-based monitoring involves the analysis of various factors that could compromise the safety of research participants. Examples include:

- High rates of S/AEs
- Numerous protocol deviations
- Unusually high enrollment rates
- Investigator experience
- Study team capability

The investigator will receive a notice that their study will be reviewed, and the pre-inspection meeting will be set up (typically) one to two weeks from the notice date. Health Canada may provide much shorter time frames (possibly even as little as 2 days) based on risk.

Pre-Inspection Meeting

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The auditor/inspector will meet with the lead investigator at the site and ask questions to get some preliminary notes regarding:

- Current status of the study (currently recruiting, data analysis, etc.)?
- How many patients have been enrolled, randomized, completed or withdrawn?
- Who identifies, contacts patients?
- How many protocol deviations?
- Etc.

The investigator should be well-versed in both the scientific concepts of the study as well as the day-to-day operations as this indicates a level of involvement.

Review – Regulatory Binder

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This involves the review of the non-patient file essential documents listed in section 8 of GCP. Examples include:

- Investigator's brochure
- Signed protocol & amendments*
- Contractual agreements
- REB approval/correspondence/annual reviews
- Regulatory approvals/amendments
- CVs/training records*
- Relevant communications (emails, meeting agendas, etc.)*
- Delegation of authority log*
- IP accountability*

* = common errors

Review – Patient Files

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The reviewer will typically randomly select a pre-determined number of patients (usually ~20%) to complete source document verification. This involves checking the patient chart against the research records for:

- Informed consent process*
- Proper data entry to CRFs
- Proper documentation and follow-up of S/AEs*
- Withdrawal procedures done correctly
- Good documentation practices*

Review - Facilities

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The reviewer may ask to look at the facilities where the research is conducted to ensure it is being done according to the requirements listed in the protocol and that all research equipment has been calibrated and located* as per protocol/SOPs. This also involves an inspection of the locations where study records* and IP* are stored.

Close-out, Report, and Follow-up

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Close-out

Following the review, the inspector will typically create a summary of findings to review with the investigator at the close-out meeting. This gives the investigator a chance to respond to any findings before the final report is written.

Audit Report

The inspector will finalize a report outlining the findings and provide to the investigator. The report will typically include a request for corrective actions to be taken and a letter in response (usually within 30 days).

Follow-up

The investigator should review the audit report and work with the team to design Corrective and Preventive Action (CAPA) plans in response to the findings. In a follow-up letter to the inspector, CAPAs should describe what the root cause of the finding was and what actions have been taken to ensure the errors will not occur in the future. The audit report and follow-up response are to be included in the regulatory binder.

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