CW-05 Randomized controlled trial in radiology research

15:20-15:40 201

Chairperson(s): Jeong Min Lee *Seoul National University Hospital, Korea*

초보연구자가 RCT를 계획할 때에 어떤 준비를 해야 하는가?

Jihoon Park

Seoul National University Hospital, Korea. pjihoon79@gmail.com

초보 연구자가 RCT를 계획할 때에 어떤 준비를 해야 하는가?

KCR 2012
Clinical Trial Workshop

분당 서울대 병원 전임의 박지훈

Contents

- Guidelines
  - CONSORT and Extensions
- 동의서
- AE reports

Guideline –CONSORT Statements

- Consolidated Standards of Reporting Trials (http://www.consort-statement.org/)

Purpose

- It offers **a standard way** for authors to prepare reports of trial findings, facilitating their **complete and transparent reporting**, and aiding their **critical appraisal** and **interpretation**

History of CONSORT

- In 1993, 30 experts met in Ottawa, Canada with the aim of developing a new scale to assess the quality of RCT reports
- Unanimous agreement steered the remainder of the workshop to focus on ways to improve the reporting of RCTs

->The Standardized Reporting of Trials (SORT) statement in 1994

- Another group, the Asilomar Working Group on Recommendations for Reporting of Clinical Trials in the Biomedical Literature, convened in Asilomar (California), USA, were working on a similar mandate

-> CONSORT Statement in 1996
-> Revised CONSORT Statement in 2001.
-> Recent CONSORT Statement in 2010

DOWNLOADS

CONSORT Statement 2010:

- *Annals of Internal Medicine*
- *BMC Medicine*
- *BMJ*
- *Journal of Clinical Epidemiology*
- *Lancet*
- *Obstetrics & Gynecology*
- *Open Medicine*
- *PLoS Medicine*
- *Trials*
- *Journal of Pharmacology and Pharmacotherapeutics*
- *International Journal of Surgery*

CONSORT 2010 Explanation and Elaboration Document:

- *BMJ*
- *Journal of Clinical Epidemiology*
- *International Journal of Surgery*

The CONSORT Statement

- The Checklist
- The Flow Diagram
- Explanation and Elaboration Document

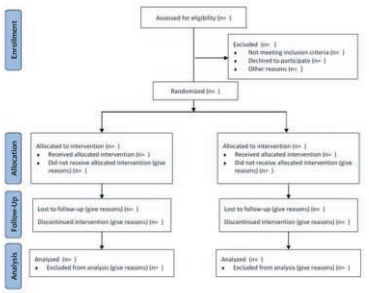
CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSORT Statement 2010 Flow Diagram



From Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.

For more information, visit www.consort-statement.org.

Table 2 | Items to include when reporting a randomised trial in a journal abstract

Item	Description
Authors	Contact details for the corresponding author
Trial design	Description of the trial design (such as parallel, cluster, non-inferiority)
Methods:	
Participants	Eligibility criteria for participants and the settings where the data were collected
Interventions	Interventions intended for each group
Objective	Specific objective or hypothesis
Outcome	Clearly defined primary outcome for this report
Randomisation	How participants were allocated to interventions
Blinding (masking)	Whether participants, care givers, and those assessing the outcomes were blinded to group assignment
Results:	
Numbers randomised	Number of participants randomised to each group
Recruitment	Trial status
Numbers analysed	Number of participants analysed in each group
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision
Harms	Important adverse events or side effects
Conclusions	General interpretation of the results
Trial registration	Registration number and name of trial register
Funding	Source of funding

BMJ 2010;340:c869

RANDOMISATION

- Three major advantages.
  - Elimination of selection bias
  - The use of probability theory
  - Blinding the identity of treatments
- Two interrelated aspects
  - Allocation concealment
  - Random sequences

BMJ 2010;340:c869

Randomisation and Minimisation

- Simple randomisation
- Restricted randomisation
- Blocked randomisation
- Stratified randomisation
- Minimisation

BMJ 2010;340:c869

Steps in a typical randomisation process

Box 3 | Steps in a typical randomisation process

Sequence generation
- Generate allocation sequence by some random procedure

Allocation concealment
- Develop allocation concealment mechanism (such as numbered, identical bottles or sequentially numbered, sealed, opaque envelopes)
- Prepare the allocation concealment mechanism using the allocation sequence from the sequence generation step

Implementation
- Enrol participants:
  - Assess eligibility
  - Discuss the trial
  - Obtain informed consent
  - Enrol participant in trial
- Ascertain intervention assignment (such as opening next envelope)
- Administer intervention

BMJ 2010;340:c869

Blinding Terminology

- Blinding
  - Single blind
  - Double blind
  - Triple blind
- Reporting blinding status

BMJ 2010;340:c869

ITT and PP

Box 6 | Intention-to-treat analysis

The special strength of the RCT is the avoidance of bias when allocating interventions to trial participants (see box 1). That strength allows strong inferences about cause and effect that are not justified with other study designs. In order to preserve fully the huge benefit of randomisation we should include all randomised participants in the analysis, all retained in the group to which they were allocated. Those two conditions define an "intention-to-treat" analysis, which is widely recommended as the preferred analysis strategy.[8 117] Intention-to-treat analysis corresponds to analysing the groups exactly as randomised. Strict intention-to-treat analysis is often hard to achieve for two main reasons—missing outcomes for some participants and non-adherence to the trial protocol.

Missing outcomes

Many trialists exclude patients without an observed outcome. Often this is reasonable, but once any randomised participants are excluded the analysis is not strictly an intention-to-treat analysis. Indeed, most randomised trials have some missing observations. Trialists effectively must choose between omitting the participants without final outcome data or imputing their missing outcome data.[119] A "complete case" (or "available case") analysis includes only those whose outcome is known. While a few missing outcomes will not cause a problem, in half of trials more than 10% of randomised patients may have missing outcomes.[120] This common approach will lose power by reducing the sample size, and bias may well be introduced if being lost to follow-up is related to a patient's response to treatment. There should be concern when the frequency or the causes of dropping out differ between the intervention groups.

Participants with missing outcomes can be included in the analysis only if their outcomes are imputed (that is, their outcomes are estimated from other information that was collected). Imputation of the missing data allows the analysis to conform to intention-to-treat analysis but requires strong assumptions, which may be hard to justify.[121] Simple imputation methods are appealing, but their use may be inadvisable. In particular, a widely used method is "last observation carried forward" in which missing final values of the outcome variable are replaced by the last known value before the participant was lost to follow up. This is appealing through its simplicity, but the method may introduce bias,[119] and no allowance is made for the uncertainty of imputation.[122] Many authors have severely criticised last observation carried forward.[119-121]

Non-adherence to the protocol

A separate issue is that the trial protocol may not have been followed fully for some trial participants. Common examples are participants who did not meet the inclusion criteria (such as wrong diagnosis, too young), received a proscribed co-intervention, did not take all the intended treatment, or received a different treatment or no intervention. The simple way to deal with any protocol deviations is to ignore them: all participants can be included in the analysis regardless of adherence to the protocol, and this is the intention-to-treat approach. Thus, exclusion of any participants for such reasons is incompatible with intention-to-treat analysis.

The term "modified intention-to-treat" is quite widely used to describe an analysis that excludes participants who did not adequately adhere to the protocol, in particular those who did not receive a defined minimum amount of the intervention.[123] An alternative term is "per protocol." Though a per protocol analysis may be appropriate in some settings, it should be properly labelled as a non-randomised, observational comparison. Any exclusion of patients from the analysis compromises the randomisation and may lead to bias in the results.

Like "intention-to-treat," none of these other labels reliably clarifies exactly which patients were included. Thus, in the CONSORT checklist we have dropped the specific request for intention-to-treat analysis in favour of a clear description of exactly who was included in each analysis.

BMJ 2010;340:c869

CONSORT extensions

Design Extensions

- Cluster trials
- Non-inferiority and equivalence trials
- Pragmatic Trials

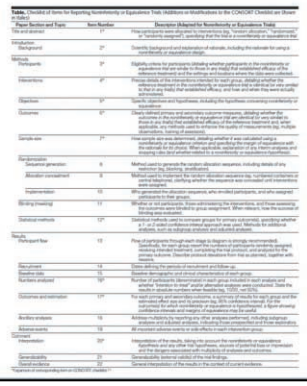
Intervention Extensions

- Herbal medicinal interventions
- Non-pharmacological treatment interventions
- Acupuncture Interventions

Data Extensions

- Harms
- Abstracts

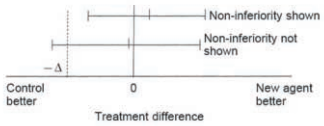
Non-inferiority and Equivalence Trials



JAMA. 2006; 295:1152-1160

Rationale for Non-inferiority or Equivalence Designs

- Determine whether a new treatment is no worse than a reference treatment
- Because proof of exact equality is impossible, a prestated margin of noninferiority (Δ) for the treatment effect in a primary patient outcome is defined



Methodological Issues

Non-inferiority and Equivalence Trials

Design

- Reference treatment
  - Efficacy should be established or in widespread use
- Both outcome measures and participants :
  - should be similar to those in trials that established the efficacy of the reference standard
- Delta
  - Smallest value that would be a clinically important effect
- Sample size
  - Δ
  - (estimated) measurement variability
  - type I error (significance criterion)
  - statistical power (or equivalently 1 – type II error)
  - paired versus parallel design
    - paired : the same group of subjects examined with both test A and test B)
    - Parallel : two separate groups of subjects, one each examined with test A and test B, respectively)

Methodological Issues

Non-inferiority and Equivalence Trials

Analysis

ITT vs. Non-ITT

- Intention-To-Treat (ITT) analysis vs. non-ITT analysis
  - In superiority test
    - 두 개의 차이를 보이고 싶은 test
    - ITT analysis 를 쓰면 두 군의 차이가 줄어듬
    - 만약 ITT analysis 에서도 똑같이 의미있게 나온다면 진짜 차이가 있다고 볼 수 있음
  - In non-inferiority or equivalence test
    - 두 개가 비슷함을 보이고 싶은 test
    - ITT analysis 를 쓰면 두 군의 차이가 줄어듬
    - 결과를 신뢰할 수 없음 (type I error의 증가)
    - Non-ITT가 deriable 할 수도 있음 (하지만, randomization 에 오류가 발생)

Methodological Issues

Non-inferiority and Equivalence Trials

Interpretation

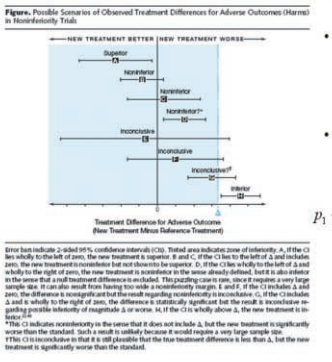


Figure. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials

Error bars indicate 2-sided 95% confidence intervals (CIs). Tinted area indicates zone of inferiority. A, If the CI lies wholly to the left of zero, the new treatment is superior. B and C, If the CI lies to the left of Δ and includes zero, the new treatment is noninferior but not shown to be superior. D, If the CI lies wholly to the left of Δ and wholly to the right of zero, the new treatment is noninferior in the sense already defined, but it is also inferior in the sense that a null treatment difference is excluded. This puzzling case is rare, since it requires a very large sample size. It can also result from having too wide a noninferiority margin. E and F, If the CI includes Δ and zero, the difference is nonsignificant but the result regarding noninferiority is inconclusive. G, If the CI includes Δ and is wholly to the right of zero, the difference is statistically significant but the result is inconclusive regarding possible inferiority of magnitude Δ or worse. H, If the CI is wholly above Δ, the new treatment is inferior.[2,4]

*This CI indicates noninferiority in the sense that it does not include Δ, but the new treatment is significantly worse than the standard. Such a result is unlikely because it would require a very large sample size.

†This CI is inconclusive in that it is still plausible that the true treatment difference is less than Δ, but the new treatment is significantly worse than the standard.

- Many noninferiority trials based their interpretation on the upper limit of a 1-sided 97.5% CI (=2-sided 95% CI)
- The 2-sided 95% CI for the outcome difference between the two groups

$$p_1 - p_2 \pm 1.96\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}$$

Pragmatic Trials

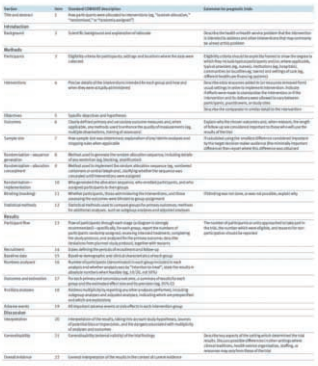
- Pragmatic trials
  - To help choose between options for care
- explanatory trials
  - To test causal research hypotheses—for example, that an intervention causes a particular biological change
- There is a continuum rather than a dichotomy between explanatory and pragmatic trials

Table 1| Key differences between trials with explanatory and pragmatic attitudes, adapted from a table presented at the 2008 Society for Clinical Trials meeting by Marion Campbell, University of Aberdeen

Question	Efficacy—can the intervention work?	Effectiveness—does the intervention work when used in normal practice?
Setting	Well resourced, "ideal" setting	Normal practice
Participants	Highly selected. Poorly adherent participants and those with conditions which might dilute the effect are often excluded	Little or no selection beyond the clinical indication of interest
Intervention	Strictly enforced and adherence is monitored closely	Applied flexibly as it would be in normal practice
Outcomes	Often short term surrogates or process measures	Directly relevant to participants, funders, communities, and healthcare practitioners
Relevance to practice	Indirect—little effort made to match design of trial to decision making needs of those in usual setting in which intervention will be implemented	Direct—trial is designed to meet needs of those making decisions about treatment options in setting in which intervention will be implemented

BMJ 2008; 337:a2390

Pragmatic Trials



BMJ 2008; 337:a2390

동의서

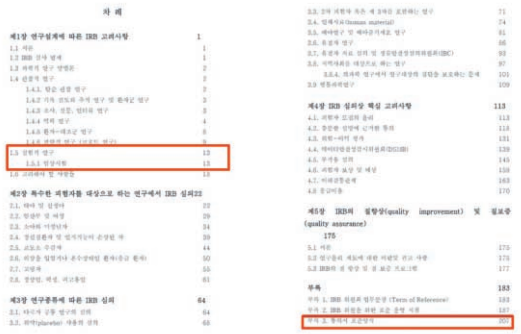
- IRB 위원을 위한 전문교재
  - 식품의약품안전청, 국립독성연구원
- 동의서 및 설명문 작성에 관한 체크리스트
  - 분당 서울대학교 병원 IRB
- A Guide to Informed Consent - Information Sheet - Guidance for Institutional Review Boards and Clinical Investigators
  - US FDA
  - http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm#general

IRB위원을 위한 전문교재

KFDA 식품의약품안전청
NITR 국립독성연구원

IRB 위원을 위한 전문교재

차 례

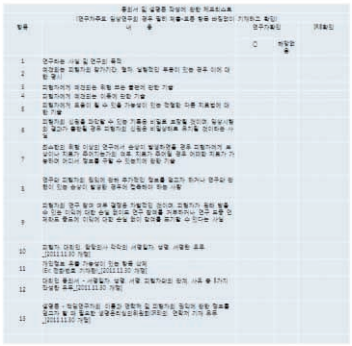


IRB 위원을 위한 전문교재

부록 3.1 피험자 설명문 및 동의서 (예시/ 성인용/ 임상 시험 분야)156)

1. 임상 연구 제목
2. 시험 책임자
3. 개요
4. 임상시험의 목적
5. 연구 약물
6. 대안 치료 (임상시험 이외의 다른 대체 가능한 치료법)
7. 임상 연구 방법에 관한 설명
   a. 절차 또는 치료
   b. 피험자 참가 기간 및 예상 피험자 수
c. 임상시험 제한 사항 및 피험자 의무
d. 시험약/대조약의 복용방법
8. 피험자에게 예견되는 부작용, 위험과 불편함
   a. 부작용
   b. 예견할 수없는 위험에 관한 설명
   c. 불편함
9. 피험자에게 예견되는 이득
10. 연구 관련 새로운 정보의 지속적 제공
11. 금전적 지급
12. 피해발생 시 피험자 보상
13. 비밀 보장
14. 자발적 참여
15. 임상시험 관련 책임자 및 연락처

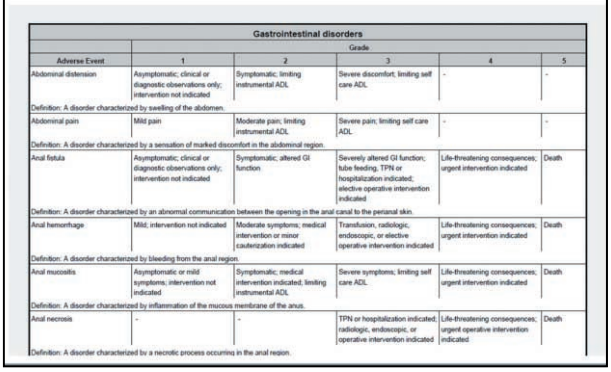
동의서 및 설명문 작성에 관한 체크리스트
-분당 서울대학교 병원 IRB



ADVERSE EVENT -terminology

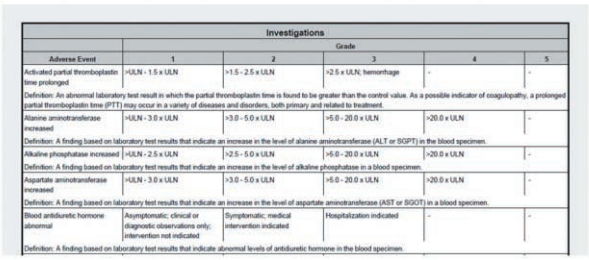
- REPORTING ADVERSE DRUG REACTIONS
  - Council for International Organizations of Medical Sciences (CIOMS)
  - http://www.cioms.ch/publications/reporting_adverse_drug.pdf
- Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
  - National Institutes of Health and National Cancer Institute
  - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

CTCAE v4.0



Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Definition: A disorder characterized by swelling of the abdomen.					
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the abdominal region.					
Anal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the opening in the anal canal to the perianal skin.					
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the anal region.					
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the anus.					
Anal necrosis	-	-	TPN or hospitalization indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the anal region.					

CTCAE v4.0



Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.					

ADVERSE EVENT -Reporting

- ADVERSE EVENT REPORTING MANUAL
  - American College of Radiology Imaging Network
  - http://www.acrin.org/Portals/0/Administration/Regulatory/ACRIN_AE_Reporting_Manual.pdf

ACRIN™
AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ADVERSE EVENT REPORTING MANUAL

ACRIN ADVERSE EVENT REPORTING MANUAL

Table of Contents

Six Categories of ACRIN Studies

- Diagnostic
- Screening
- Interventional
- Investigational Agents
- Investigational Devices
- Collaborative

TABLE A *[use for NON-radioactive imaging agents and studies that do not use imaging agents]*
All Phases
AdEERS reporting requirements for AEs occurring within 30 Days of the last study related procedure

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unexpected	Expected	Unexpected	Expected
		with Hospitalization	without Hospitalization		with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	Not Required	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Thank you for your attention