THE BENEFITS AND CHALLENGES OF PERFORMING A CENTRAL REVIEW OF RESPONSE IN A CHRONIC LYMPHOCYTIC LEUKAEMIA TRIAL

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Society of Clinical Trials (SCT)
21/05/2013

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Accurate Measurement of Trial Endpoints

Critical to:

- Ensuring that true treatment effect is being observed
- Providing a reliable answer to the research question
- Integrity of the trial
- Treatment of current and future patients

Central Review of Endpoint Data

Independent blinded assessment of the primary and in some instances the key secondary endpoint data, by a carefully selected panel of clinical experts.

Increases the accuracy and reliability of your endpoint data and strengthens trial results

Benefits of Performing a Central Review of Endpoint Data

Beneficial for:

- Subjective endpoints - prone to assessor bias/error and inconsistencies in reporting
- Open trials (i.e. treatment allocation is known)
- Multi-centre trials

- Control for local assessment bias

- Ensure consistency in the assessment of endpoint data

- Increase the accuracy of the assessment of the endpoint data and strengthen the trial results

Central Review of Response in a Phase II Trial in CLL

- Interim analysis of a phase II, multi-centre, open, randomised-controlled trial in patients with previously untreated Chronic Lymphocytic Leukaemia (CLL)
- Randomised on a 1:1 basis to the standard control or experimental arm
- Primary endpoint – proportion of participants achieving a Complete Response at 3 months post-therapy
- Complete response is evaluated using the bone marrow and other clinical parameters, according to the IWCLL Response Criteria guidelines

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Central Review of Response in a Phase II Trial in CLL

Complete Response assessed via the IWCLL criteria:

- Complete Remission (CR)
- Complete Remission with incomplete marrow recovery (CRi)

Achieved a Complete Response

- Partial Remission (PR)
- Stable Disease (SD)
- Progressive Disease (PD)

Did not achieve a Complete Response

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Central Review of Response in a Phase II Trial in CLL

- Decision to perform a central review of the primary endpoint data was agreed and costed for at the grant application stage
- Once the trial funding was in place, a central review panel was established consisting of expert CLL clinicians, independent from the trial
- Data required to assess response was collated, blinded and sent to two independent reviewers for an assessment of response
- If in the event that the two initial assessments did not agree, a third arbiter was in place to make a final decision on response

Independent Central Assessment of Response

98 participants response to therapy were centrally reviewed:

- 76 cases (78%) - initial two reviewers assessments of response were concordant
- 22 cases (22%) – arbiter was required to make a final decision on response

Concordance of Local and Central Assessments of Response

		Central Review		
		CR	Not CR	Total
Local Review	CR	**54 (73%)**	**20 (27%)**	74 (100%)
	Not CR	**8 (40%)**	**12 (60%)**	20 (100%)
	Total	62 (66%)	32 (34%)	94 (100%)

- Of the 74 CRs reported locally, the central reviewers agreed 73% of the time
- Of the 20 non-CRs reported locally, the central reviewers agreed 60% of the time

- Trend towards local reviewers reporting a higher number of Complete Responses (74 vs. 62)

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Benefits and Challenges of Performing a Central Review of Response in CLL

Challenges	Benefits
Time consuming	Increased the consistency and accuracy in the reporting of the primary endpoint
Logistically complex	Sought to eliminate local site assessment bias
Issues with missing data	Strengthened the interim analysis results

Points for Consideration

- Consider the appropriateness of performing a central review of your endpoint data:
  - Is the endpoint subjective and thus subject to site bias and inconsistencies in reporting?
  - Is it a complex endpoint subject to assessment error?
  - Size of trial
  - Phase of the trial

- Logistical issues / practicalities – establish processes at the trial design stage and set-up as soon as funding is in place

- Costs / man-power - plan for at the trial design stage

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THANK YOU!