Tissue-Engineered Skin in Burn Management and Research – How to Collect the Evidence

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Background:

Evidence for a clinical trial should be difference than evidence for a lab test. Well-designed clinical trial must collect evidence that sheds light on outcomes.

"Outcomes are not "outputs"; they are not lab results; they are not technical details. They're real-world results, like physical functioning or level of pain. How soon after treatment can a patient with low-back pain expect to return to work? How likely is a man to experience incontinence or sexual dysfunction after treatment for prostate cancer? These are questions about outcomes. Unfortunately, today, in health care systems around the world, evaluation efforts take into account a number of clinical indicators, structural metrics, and even reputation – but they tend to ignore outcomes."

- Michael J. Porter – Harvard University & ICHOM

The primary endpoint of confirmatory phase 3 trials should represent something that MATTERS TO A PATIENT.

How to design an effective trial and collect evidence:

1. Define the primary endpoint in line with the question to be answered by the trial.
2. Use validated tools to measure characteristics of the primary end point.
3. Even with validated tools, use of such tools in multicenter and multinational trials requires specific training and evaluation of the outcomes.

Expansion of each step:

1. Define the primary endpoint in line with the question to be answered by the trial.

In designing a protocol, we must consider what we're designing:

Is it a phase one safety trial? Is it a phase 3 confirmatory trial? What kind of question are we trying to answer? This must be clear.

Characteristics of outcome/endpoint measures:

- Easy to diagnose: easy to identify; no evaluator judgment needed
- Free of measurement error: reliable with repeated measure
- Internal validity: directly linked to property of interest
- External validity: ability to generalize to a wider population

For trials related to wounds, endpoints and evidence will be related to:

- Safety
- Wound healing
- Rate of wound closure
- Quality of wound healing
- Cost effectiveness

Case study example:

Clinical trial intended to prove ability to reduce scarring and improve scar quality of large burns by adding cultured epithelial cells. Patients received standard treatment on one burn and SSG mesh with cultured autologous keratinocytes on another, comparable burn. Each patient acted as his own control.

Outcomes related to epithelialization and reduction of scarring. Primary outcome: % epithelization after 5-7 days post-op.

We also wanted to assess the level of scarring. We used the POSAS (Patient and Observer Scar Assessment Scale) assessing vascularity (through color), pigmentation, thickness, relief, pliability and surface area of the scar.

2. Use validated tools to measure characteristics of the primary end point.

"To measure is to know. If you cannot measure it, you cannot improve it."

– Lord Kelvin

Case study example:

Used DSMII (Cortex Technology, Denemarken) & Colorimeter (Courage & Khazaka, Duitsland)

E/M, LaB, RGB, XYZ ITA

Reliability: Good

Validity: Good (DSMII > Mexameter > Colorimeter)

3. Even with validated tools, use of such tools in multicenter and multinational trials requires specific training and evaluation of the outcomes.

Case study outcome:

There WAS a slight but significant improvement in epithelization (6%) at 6 days post-op.

More importantly, 12 months later, improvement was even more significant (18-33% improvement on all POSAS criteria). Scar color and pigmentation as measured by dermaspectrometer showed improvements over control of 20-31% at 3 months and 39% at 12 months.

Wound healing rates and scar quality rates were both improved from this trial.