### PEBLES: natural history of RDEB DEBRA International Zagreb September 2016

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## Clinical trials in EB

- Clinical trials need endpoints
- Endpoints need to be well-defined and reliable
- Need to know that they reflect what you are interested in
- Need to be able to detect change over time



## Clinical trials in EB

- Endpoints to assess treatment benefit
  - Life expectancy
  - Disease complications
  - How the patient feels or functions
- Clinical outcome assessments
  - Patient-related
  - Clinician-related
  - Observer-related
- Biomarkers



### Clinical trials in EB

- Endpoints can be difficult to define in EB clinical trials:
  - Different types
  - Different problems
  - Differences depending on age
  - Confounders
  - Rare disease



• What should we choose?

Objective Blister counts? Surface area? Blood tests? Suction blister time?

Subjective Pain score? Itch score? Quality of life?

Severity score BEBS? EBDASI? iSCOREB?

- The route to well-defined and reliable endpoints begins with an understanding of the disease
  - How does EB affect someone?
  - How does that change over time?
  - Is an intervention or treatment affecting the disease trajectory?



 Need to understand the natural history of EB



- Need for reliable and quantifiable outcome measures for development of novel therapies in EB
- Requires in-depth understanding of the natural course of EB.....
- Acquisition of cross-sectional and prospective data from a cohort of EB patients
- Initially in different types of RDEB









### Neonate





### Childhood





### Adult

- 2 phases to the study
  - Literature review of existing material about complications and natural history of EB
  - Prospective data-gathering from RDEB patients seen at London EB centres of clinical, laboratory and health economic parameters











- 586 articles
- Most relevant information from National EB Registry in US
  - Covers most systems
  - Has a denominator: prevalence and cumulative risk data
- Otherwise individual cases or small series

- EB SCCs
  - mean age of first SCC in GS-RDEB 28.6y (6-48y)
- Cardiomyopathy
  - Mean age 11.6y (2-28y)
  - Death in 9/20, mean 0.5y after diagnosis
- Dysphagia
  - Mean age of onset in GS-RDEB 18.2y (7-41y)
- Gastrostomy tube insertion
  - Mean age 8.2y (0.4-18.5y)

- Small numbers not large series
- Prone to reporting bias
- Specific type of RDEB often not stated
- Different subtypes of RDEB lumped together
- Description of an existing complication but not when it started or how it progressed
- Very poor description of the natural history highlighting the need for research





- Prospective
- **E**pidermolysis
- Bullosa
- Longitudinal
- **E**valuation
- Study

Recessive dystrophic EB

- Type of RDEB and lab data
- Clinical aspects
- Laboratory results and investigations
- Disease severity scores
- Subjective scores
- Photographs of skin
- Economic costs

- Company employed to devise data capture tool
- Tablet device with questionnaires
- Up to 2000 possible data entry points per patient





- Patients/parents sent booklet of questionnaires to complete before review by researcher
- Age appropriate scores e.g. QOL, puberty, pain
- Also sent a camera for standard view photographs

- Demographics
  - Name and DOB
  - Gender
  - Type of EB
  - IF and mutation results
  - Ethnicity
  - Family history
  - Social history
  - School/work

Skin

- Body map wounds etc
- Blister count
- Photographs
  - Standard views on tablet or own camera
- Growth/development
  - Ht and Wt
  - BMI
  - Pubertal stage

- Dental
  - Caries/missing teeth
  - Microstomia
  - Dental surgery



### Hands

- Hand contracture/flexion
- Splints
- Previous surgery



- Mobility
  - Fully mobile
  - Limited walking
  - Walking around the house
  - Wheelchair dependent
- Eyes
  - Symptoms

### • ENT

- Symptoms
- Interventions

- Gastrointestinal tract
  - Dysphagia
  - Aspiration
  - Previous ODs
  - Nutrition
  - Oral/tube feeding
  - Bowel habit
  - Colitis



### Cancer

- Age at first SCC
- Numbers/ sites of SCCs
- Local/regional/dista nt spread
- Therapies
- Other cancers

### Severity scores

- iSCOREB
- BEBS





## **PEBLES:** laboratory data

- Haematology
  - Hb
  - lron
  - Ferritin
- Renal
  - Urinalysis
  - BP
  - Renal function

- Inflammatory status
  - CRP
  - ESR
  - Ferritin
  - Platelet count

### Serum stored

## **PEBLES:** laboratory data

- Endocrine/bone health
  - Calcium
  - Vitamin D
  - Spine X-ray
  - DEXA scan

- Nutritional
  - Albumin
  - Vitamin D
  - Selenium
  - Zinc



- Cardiology
  - Echocardiogram



### **PEBLES:** subjective data

- Pain questionnaire
  - Procedural pain
  - Background pain

# Quality of life score PEDSQL QOLEB

Itch questionnaire
Leuven itch score



## PEBLES: health economic data

- Hospital appointments
  - Numbers
  - Admissions
  - Length of stay
- Medication
  - Types and route



## PEBLES: health economic data

- Dressings
  - Types
  - Sizes
  - Numbers used per week
  - Linked to costs
- Dressing changes
  - Who does them?
  - Paid?
  - Hours/week





### EB Natural History Project



Guy's and St Thomas' MHS





### EB Natural History Project



### 9. In the past month, how did your itching manifest itself?





### EB Natural History Project







### **EB Natural History Project**



External ear - Left



- Data collection repeated every 6 months (up to 10y age) or 12 months (over 10y)
- Redesigning as a web-based system which will be more robust to handle so much data
- Retrieve data via a dashboard to interrogate different variables

### PEBLES: where are we now?

- 54 consented patients
- 10 children, 44 adults
  - 46 completed data for 1<sup>st</sup> assessment
  - 26 completed 2<sup>nd</sup> assessment
  - 2 completed 3<sup>rd</sup> assessment
  - I completed 4<sup>th</sup> assessment







Avg BMI By Age Group



Q041 Sub-type\_RDEB 50 · RDEB - I RDEB - O 45 -RDEB - Pr 42.04 RDEB - Sev Gen 40 37.1<u>9</u>6.50 37.31 35 -31.31 29.63 30 -25.70 25 · 22.90 22.97 19.54 20.06 19.00 20 · 17.00 6.00 15 -9.38 10 · 5 · 0 · 0-16 17-25 26-35 36-45 56-65 Age\_Group\_v3 46-55 66-76

### Avg BEBS Score By Age Group



### Background & Procedural Pain

### Avg Haemoglobin by Age Group









A Total of £1,855,766 per Year for dressings





### A Total of £443,739.9 per Year for dressings RDEB - Sev Gen

### Research\_No





### Dress Hours a Week x Care Cost Per Hour x 52 Weeks



Total duration of stays since last review (in days) - Cost @ £212.00 a Day With RDEB - Sev Gen



- More detailed information about RDEB than previously collected
- Comprehensive picture of all aspects of well-characterised RDEB patients
- Will extend to other centres
- In time, for other types of EB

Identify meaningful endpoints for future clinical trials

## **PEBLES:** natural history of EB



## Any questions or comments?

