AKU International Patient Workshop 2024

AKU

Alkaptonuria Society

Housekeeping

Please note, there is no fire drill planned at the hotel today. If the fire alarm sounds, please walk out to the coffee area and take the stairs left of the coffee stations.

If you would need assistance, please fill out the fire procedure from - we will collect these and give these to the hotel team.

The International AKU Patient Workshop

Dr Nicolas Sireau,

Chair & CEO, AKU Society

nick@akusociety.org

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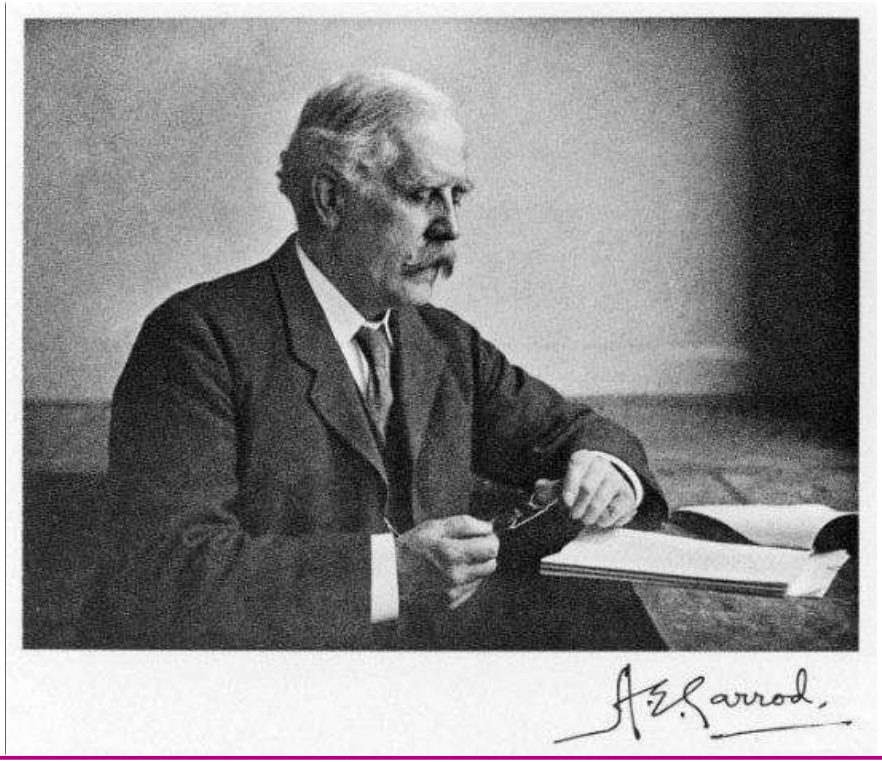
1902: Sir Archibald Garrod



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The Croonian Lectures

ON

INBORN ERRORS OF METABOLISM.

Delivered before the Royal College of Physicians of London on June 18th, 23rd, 25th, and 30th, 1908,

BY ARCHIBALD E. GARROD, M.A., M.D. OXON., F.R.C.P. LOND.,

ASSISTANT PHYSICIAN TO, AND LECTURER ON CHEMICAL PATHOLOGY AT, ST. BARTHOLOMEW'S HOSPITAL; SENIOR PHYSICIAN, HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET.

LECTURE II.[1]

Delivered on June 23rd.

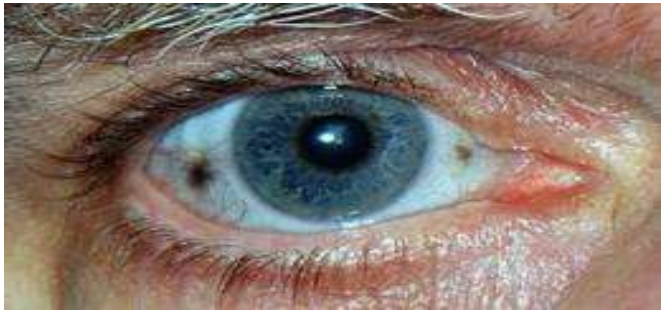
ALKAPTONURIA.

MR. PRESIDENT AND FELLOWS,—Of inborn errors of metabolism, alkaptonuria is that of which we know most, and from the study of which most has been learnt. In itself it is a trifling matter, inconvenient rather than harmful, which only attracts attention because an infant stains its clothing, or because an adult fails to effect an insurance of his life. The medical man merely needs to be aware of its existence and to be acquainted with the methods for its recognition in order that he may not mistake it for troubles of graver kinds; but for the chemical physiologist and pathologist it is one of the most interesting of metabolic

the early years of the ninete
was drawn in medical writing
black when passed and such as
but it is difficult to suggest an
alkaptonuria for some cases
sixteenth and seventeeth centur
G. A. Scribonius[4] (in 1584) of a
enjoyed good health, continuou
that cited by Schenck[5] (in 160
similar peculiarity and stated
life. The most interesting reco
in the work of Zacutus Lusitan
patient was a boy who passed
age of 14 years, was submitted
ment which had for its aim the
his viscera, which was supposed
in question by charring and
the measures prescribed were
cold and watery diet, and drug
any obvious effect, and eventu
the futile and superfluous thera
their natural course. None of
married, begat a large family,
life, always passing urine black

That alkaptonuria is a very
question, and many medical n
never met with it. Of its occ
a family and of its mode
spoken at sufficient length in
majority of instances it is pre
throughout life, but has been s

The AKU Tetrad



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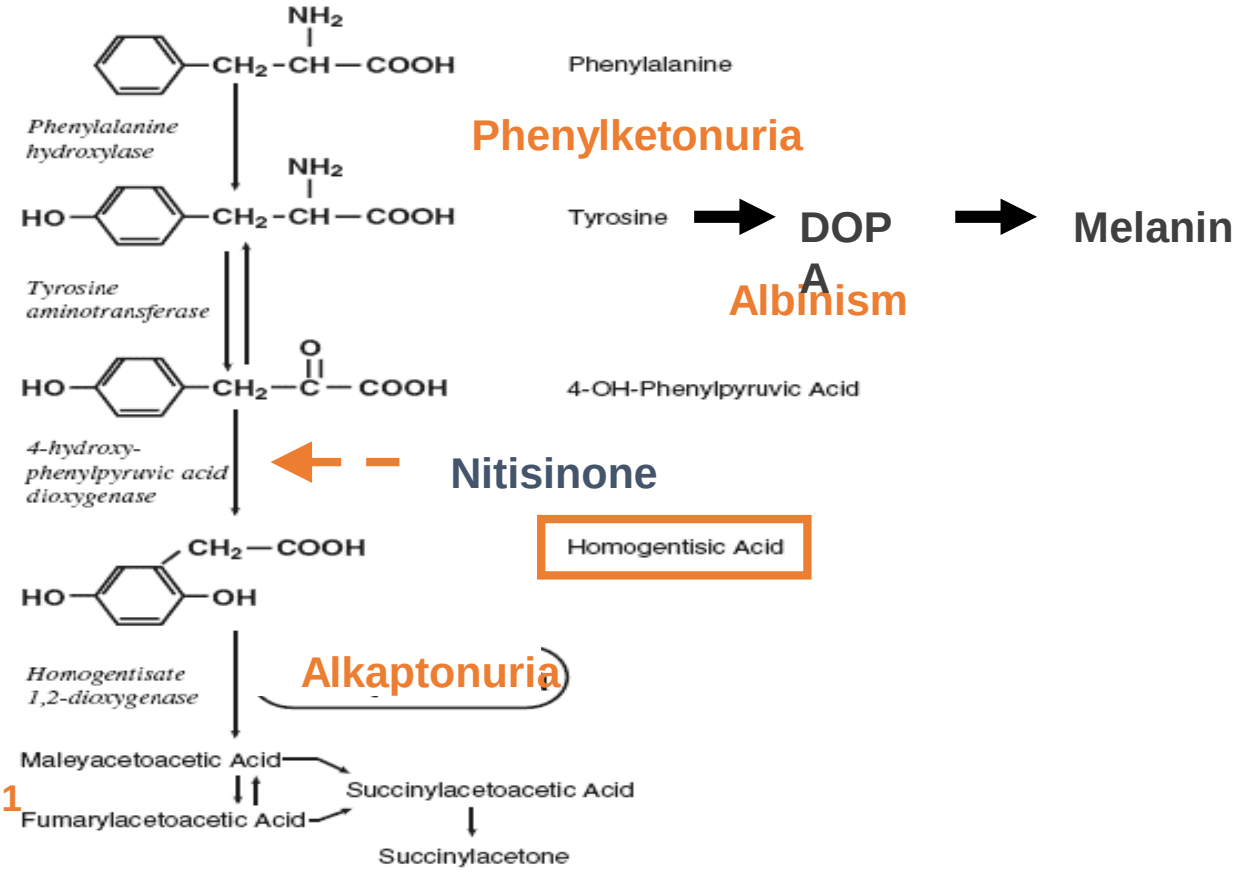
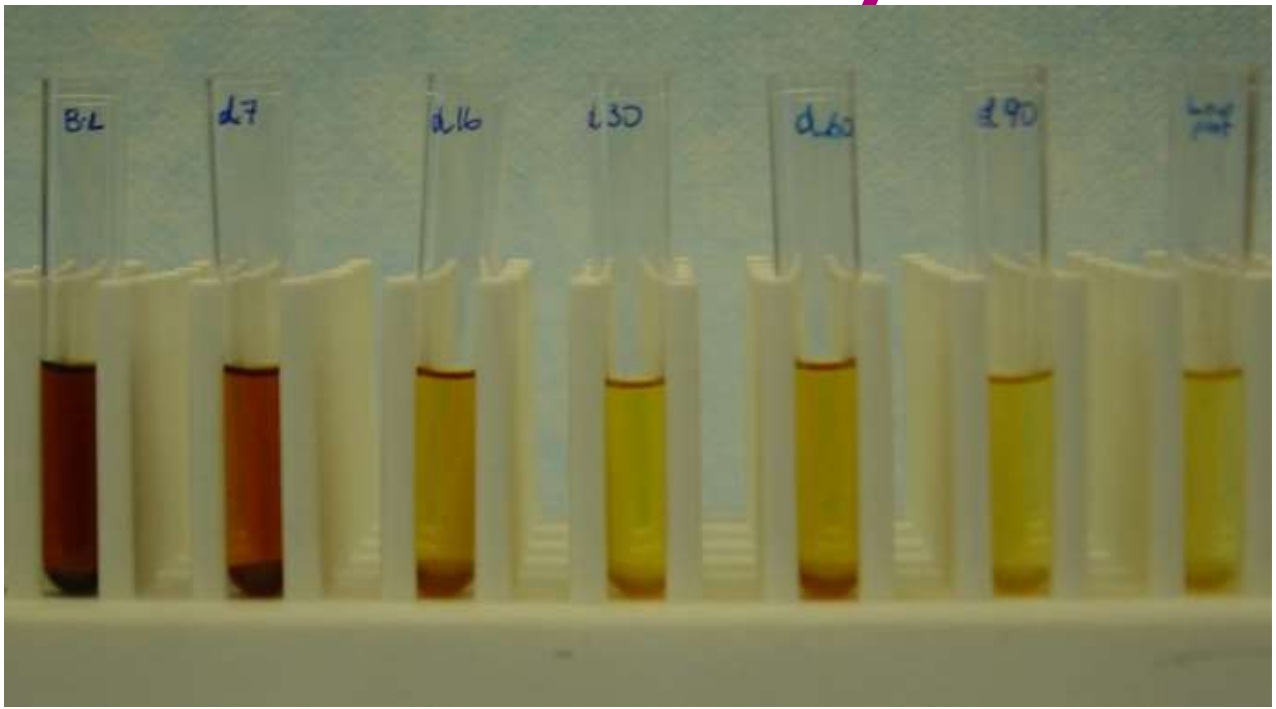
Metabolic pathway

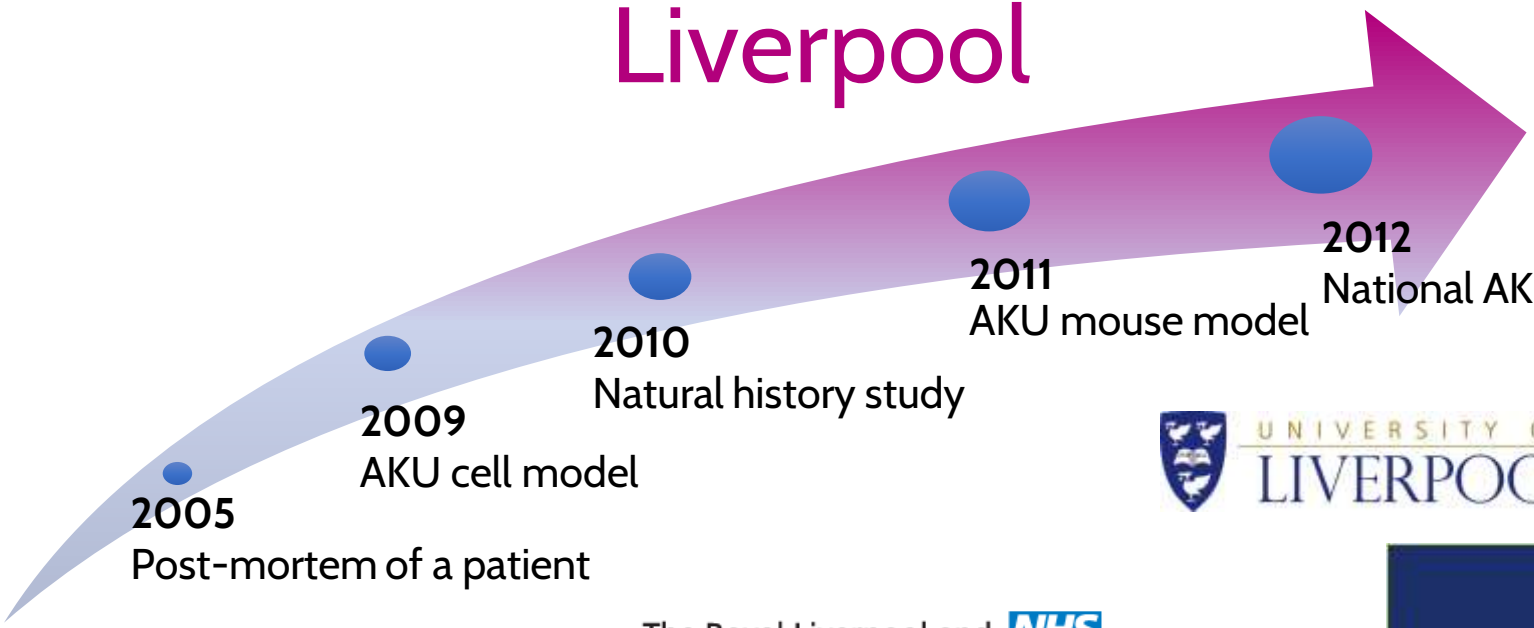


Urinary HGA



AKU Mouse Model

AKU Academic Research In Liverpool



UNIVERSITY OF LIVERPOOL

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

liverpool JMU

AKU Alkaptonuria Society

Credit to Prof L Ranganath, Prof Jim Gallagher and Prof Jonathan Jarvis

1325 AKU Patients World Wide

AKU Societies in EU, Asia, Middle East and North America

- AKU Society UK
- ALCAP (France)
- AIMAKU (Italy)
- AKU Society Germany
- AKU Society Netherlands
- AKU Society Jordan
- AKU Society India
- AKU Society Slovakia
- AKU Society North America (USA and Canada)
- AKU Society Belgium
- AKU Society Sweden
- AKU Society Asia

AKU
Alkaptonuria Society

The National AKU Centre at the Royal Liverpool University Hospital

AKU
Alkaptonuria Society


The Robert Gregory National Alkaptonuria Centre

The clinical trials

DevelopAKUre

DevelopAKUre Consortium

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

Hôpital Necker Enfants Malades

Národný ústav reumatických chorôb

Clinical Sites

AKU Alkaptonuria Society

ALCAP Association pour la Lutte Contre l'Alcaptonurie

Patient Support

Regulatory & Monitoring

PSR theorphanEXPERTS

sobi Swedish Orphan Biovitrum

Analysis

University of Liverpool

Slovak Academy of Sciences

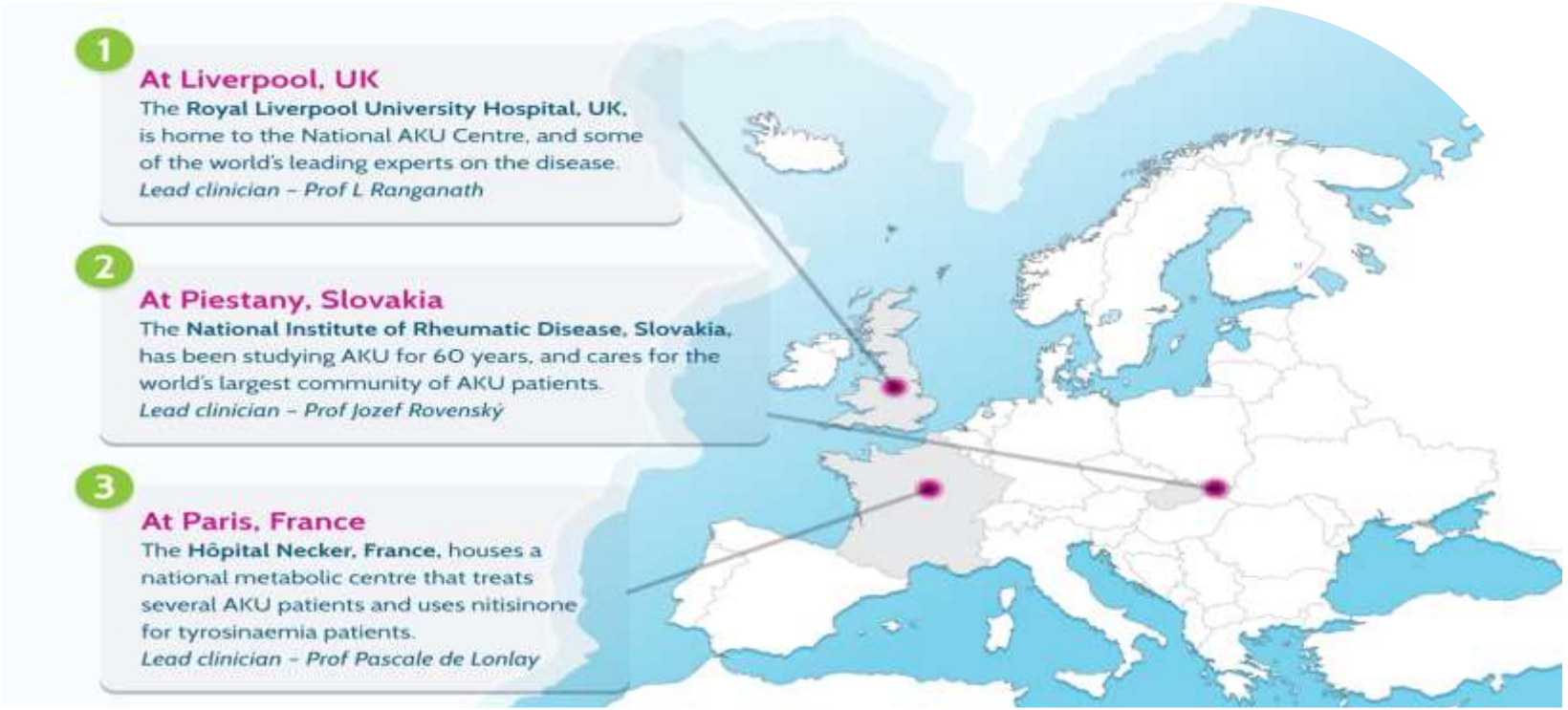
Università di Siena 1240

Nordic Bioscience

Three Studies

Trial Name	Description	Sites
SONIA 1: Suitability of Nitisinone in Alkaptonuria 1	3-month phase II study	UK/Slovakia
SONIA 2: Suitability of Nitisinone in Alkaptonuria 2	4-year phase III	UK/Slovakia/France
SOFIA: Subclinical Ochronosis Features in Alkaptonuria	Cross-sectional study	UK

Clinical Sites



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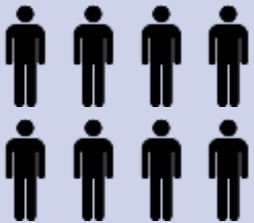
SONIA 1

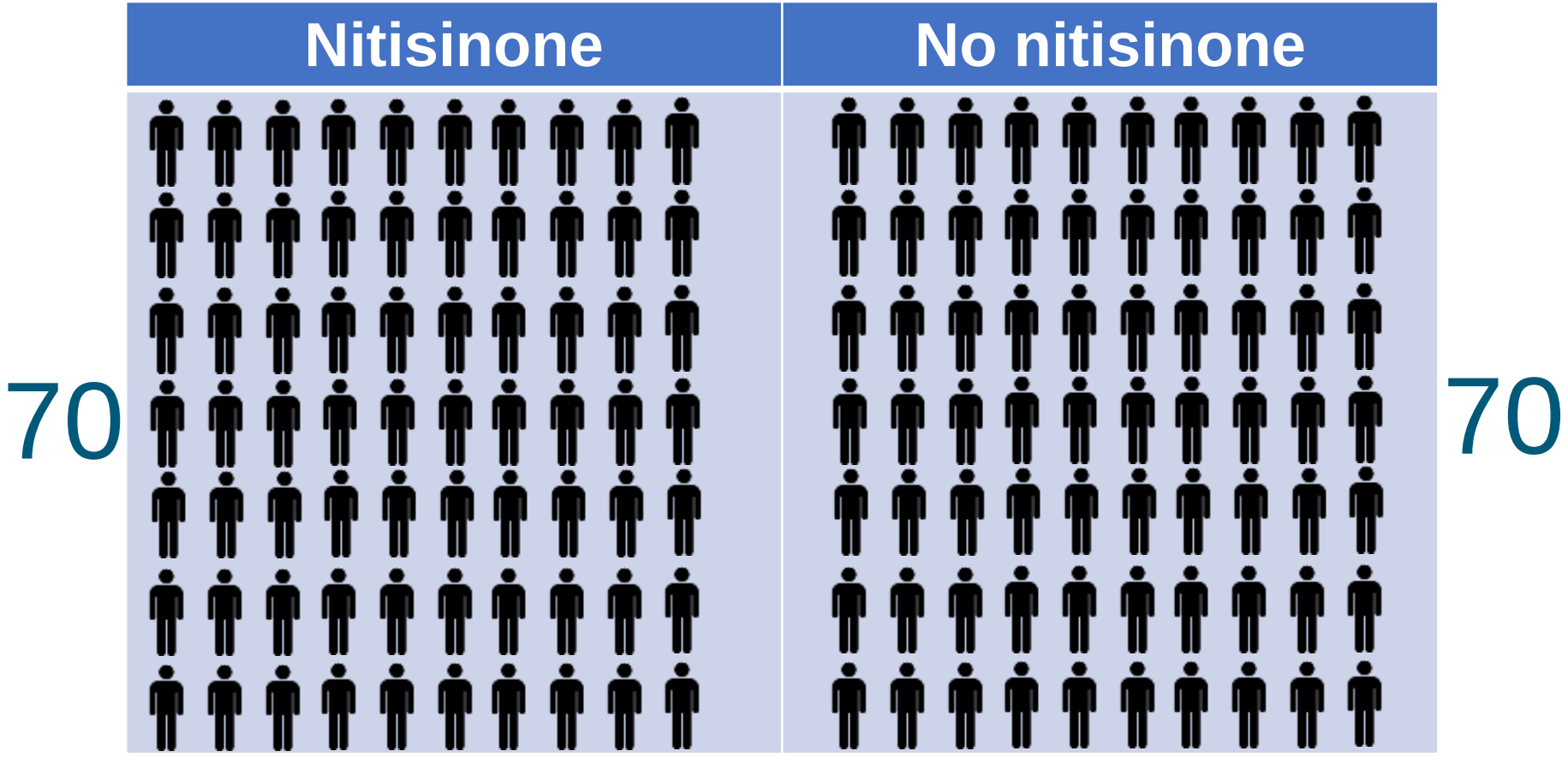
0mg	1mg	2mg	4mg	8mg
				

SONIA 1 results

0mg	1mg	2mg	4mg	8mg
				
0%	**87.6%**	**95.1%**	**97.3%**	**99.4%**

DevelopAKUre

SONIA 2



138 Patients

9 Months

Statistical significance reached!

EMA provides positive opinion!

EC grants marketing authorization!

"These trials have given us great hope. This treatment could completely change our lives. We're that one step closer to a cure."

- Belgium AKU patient

Current research

- Tyrosine inhibitors – pre-clinical success
- mRNA therapy – early pre-clinical stage
- Gene therapy – planning stage

- The workshop programme
- Expenses reimbursement

Dr Nicolas Sireau,
Chair & CEO, AKU Society
nick@akusociety.org

www.akusociety.org

Group A - Please go to Shanghai Suite for the cooking demonstration with Natasha Beatty, Nutricia.

Group B - Please stay seated here for the next session - Diet & AKU with Clare Soulsby, NAC Dietician

Diet and Alkaptonuria

Clare Soulsby

AKU Dietitian

The Robert Gregory National AKU Centre (NAC)

The Robert Gregory
National AKU Centre

NHS
Liverpool University Hospitals
NHS Foundation Trust

DIETARY MANAGEMENT OF AKU

Current dietetic management at NAC

- 2-10mg Nitisinone
- Dietary protein 0.75-0.83g/kg (UK RNI/ WHO)
- Intakes 40-65kg protein/day
- Dietary management:
  - 70% high biological value protein (7g protein swaps)
  - 30% low biological value protein (2 g protein swaps)
  - Fruit and vegetables freely
  - Tyrosine/ phenylalanine free protein drinks if high serum tyrosine
- Aim: serum tyrosine <700umol/L

7g PROTEIN SWAPS

25g meat/chicken
40g fish
25g cheese
200ml milk
125mls yoghurt
1 egg

2g PROTEIN SWAPS

½ slice bread
30g cooked pasta
125g boiled potatoes
60g chips
75g cooked rice
20g oats

Dietary management of AKU in other countries

- Most use 10mg of Nitisinone

Dietary management:

- 0.83g/kg (40-65g/d) protein
- TYR/ PHE free drinks?

OR

- Low protein diet (10-20g/day)
- TYR/ PHE free drinks provide 40-60g (2-3 sachets/ pouches)

OR

- Plant based

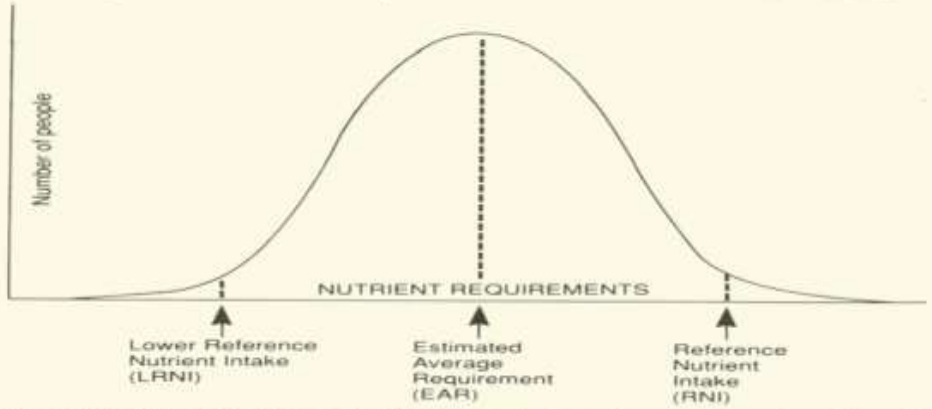
HOW MUCH PROTEIN DO ADULTS NEED?

Why 0.75g protein/kg

- UK dietary reference value = 0.75g/kg
- WHO = 0.83g/kg
- Based on nitrogen balance studies in healthy young lean individuals

Why 0.75g protein/kg

Figure 1 Relationship between various reference values



The Lower Reference Nutrient Intake is enough for only a small number of people (about 3% of the population who have low needs). It is not enough for most people.

The Estimated Average Requirement for energy or a nutrient is the amount which any stated group of people will, on average, need.

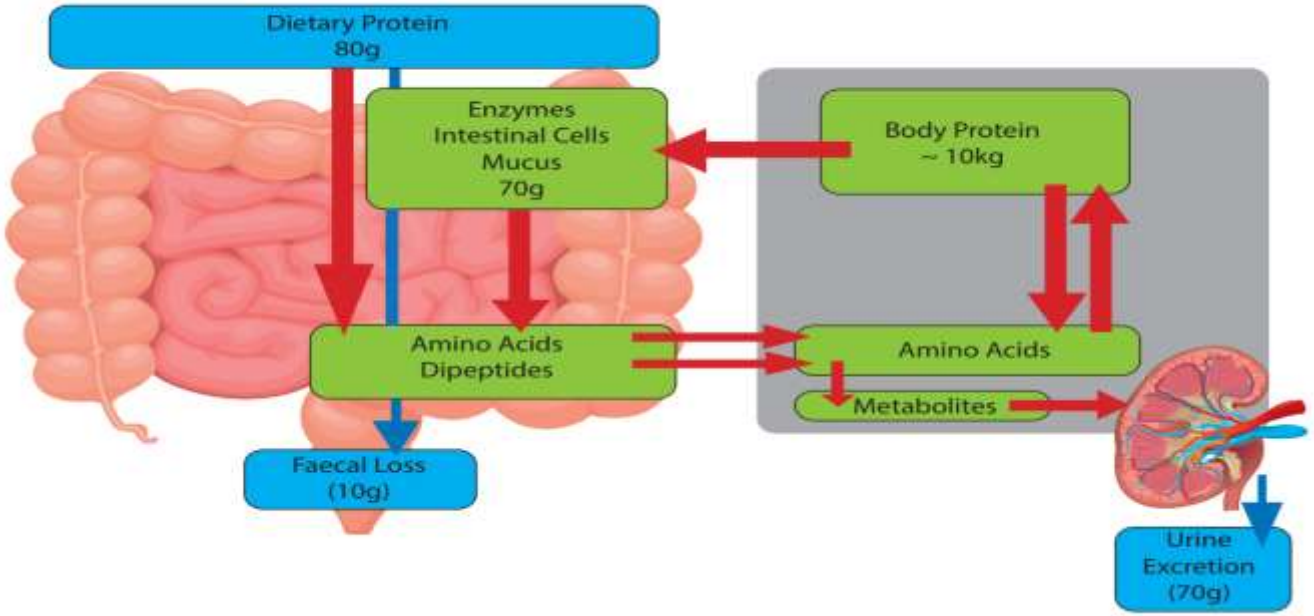
The Reference Nutrient Intake is the amount of a nutrient which is enough for at least 97% of the population.

Nitrogen Balance

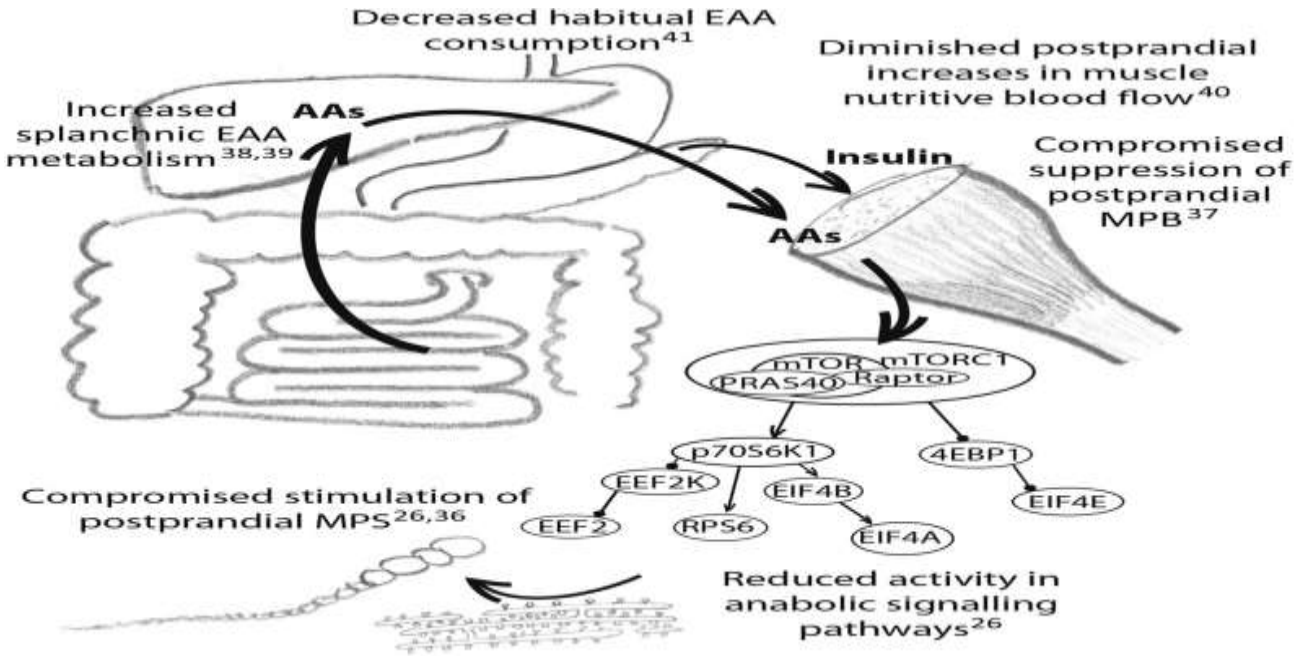
nitrogen intake	vs	nitrogen losses
(dietary protein)		(faecal losses)
		(urine losses)
		(cells, mucous etc)

nitrogen intake = nitrogen losses

Nitrogen Balance



Nitrogen utilisation in the elderly



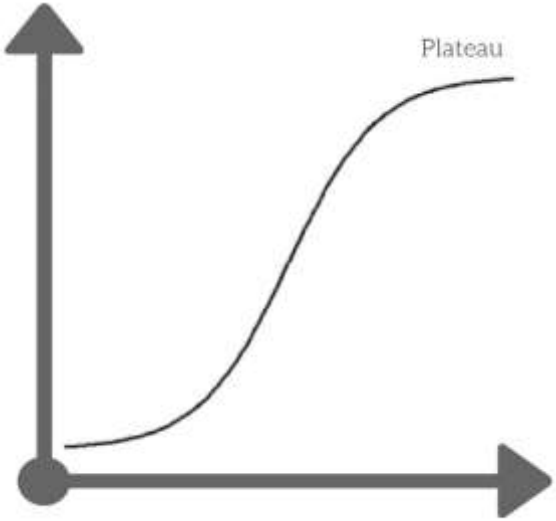
Protein requirements

May be higher in:

- The elderly (>55years)
- Disease/ metabolic stress
- ? Athletes

Need to be adjusted in

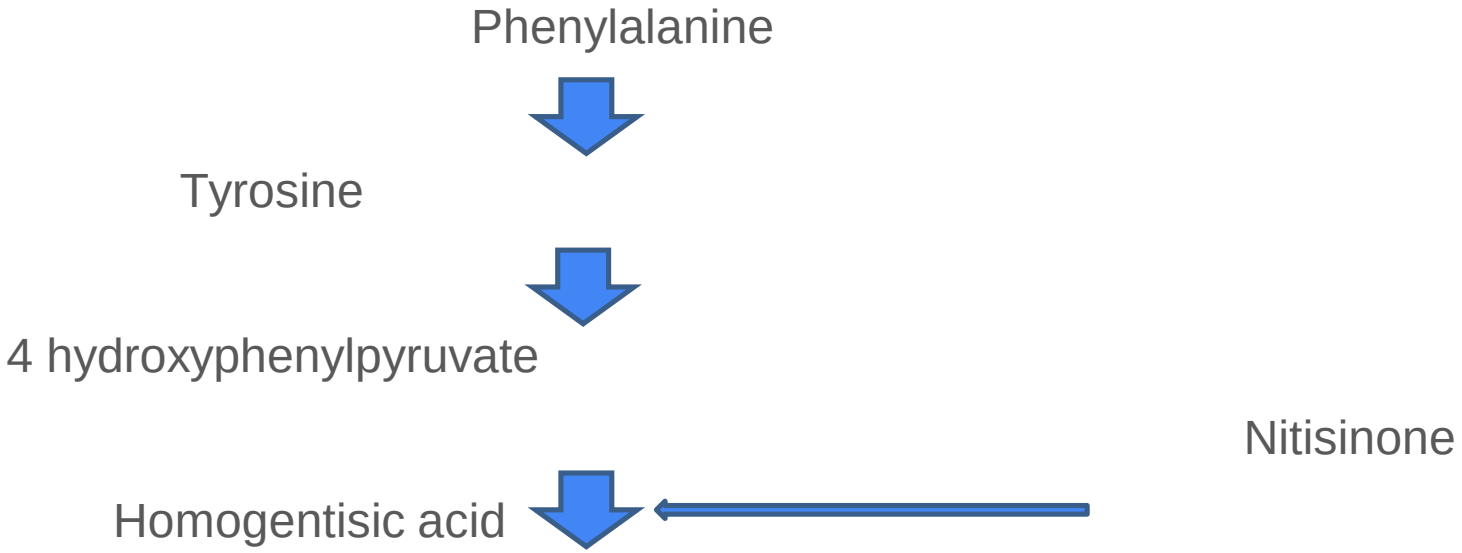
- Underweight
- Overweight



What is dietary protein

Protein is made from 22 amino acids

- 9 are essential - so must come from our diet.
- Phenylalanine and tyrosine are found in all protein containing foods
- They are used to make serotonin and melanin and thyroid hormones


Phenylalanine
Tyrosine
4 hydroxyphenylpyruvate
Nitisinone
Homogentisic acid

What is dietary protein

Summary

- 0.75-0.83g/kg meets the needs for most
- Adjustments in elderly and extremes of BMI
- Use of TYR/PHE free as additional protein

DIETARY STRATEGIES TO REDUCE HIGH SERUM TYROSINE LEVELS

Adherence to diet

NUTRITICS

plans which will have greater impact.

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Liverpool University Hospitals
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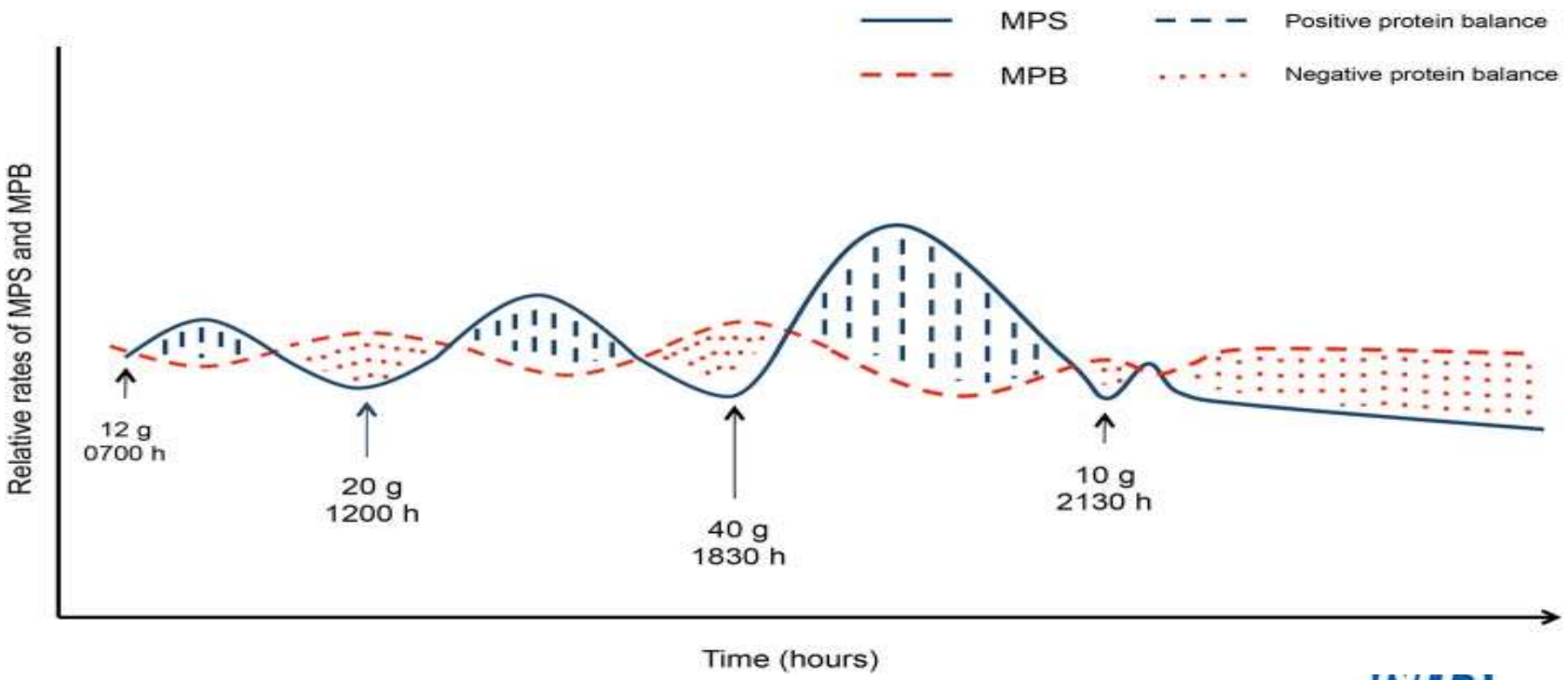
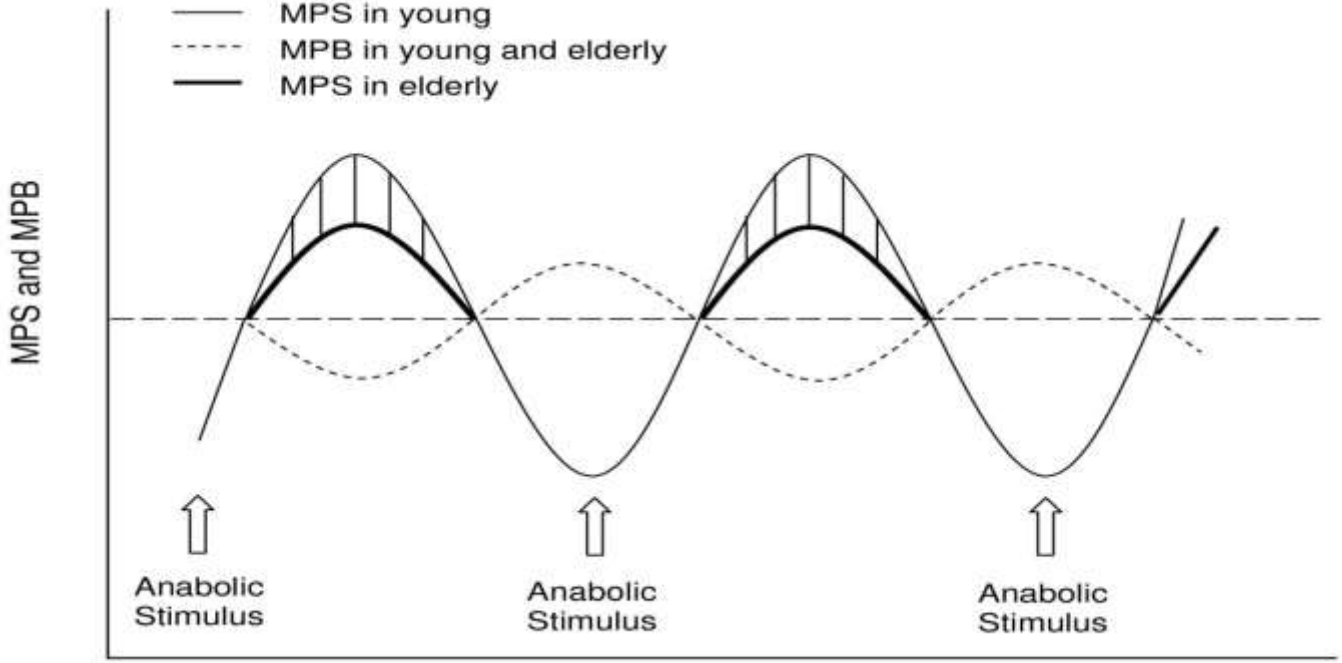
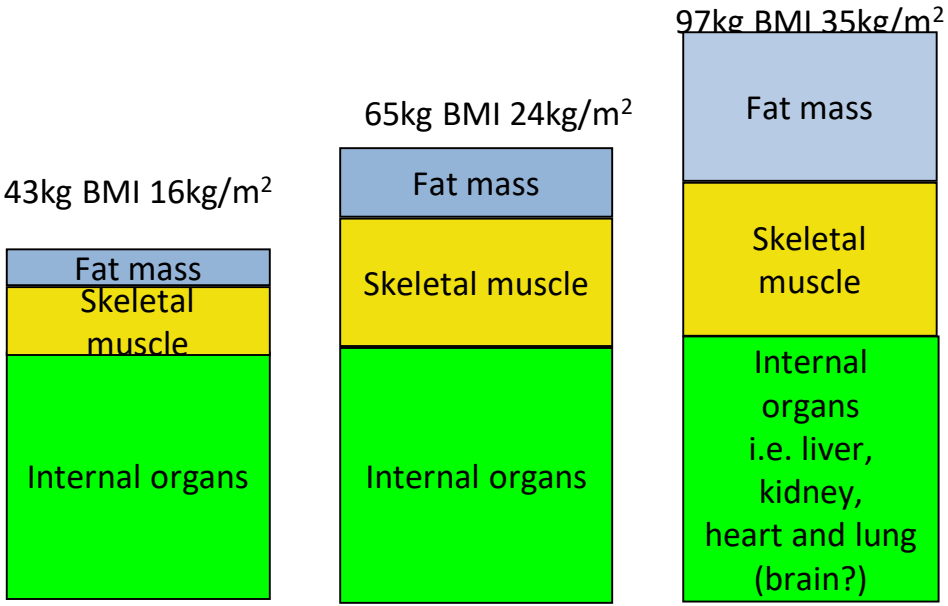
Protein utilisation by muscles




MPS in young
MPB in young and elderly
MPS in elderly
MPS and MPB
Anabolic Stimulus
Anabolic Stimulus
Anabolic Stimulus

Tyrosine/ phenylalanine free protein substitutes

Dietetic strategies for hypertyrosinaemia: extremes of BMI and lean body mass



- 97kg (BMI of 35) = 73g protein
- 65kg (BMI of 24) = 49g protein
- 43kg (BMI of 16) = 32g protein

Horgan GW & Stubbs J (2003): European Journal of Clinical Nutrition 57(2), 335-340

Dietary strategies to reduce high serum tyrosine levels

- **Dietary adherence:**
- Protein intake of 0.75-0.83g/kg/day
- Adjusted for extremes BMI
- Good spread of protein
- Increase exercise
- **High tyrosine despite dietary adherence:**
- Add tyrosine free protein substitute
- Increase exercise
- Reduce Nitisinone
- Or reduce protein intake and increase tyrosine free protein substitutes

Really good podcast

- https://zoe.com
- ZOE Podcast: Should I eat more protein
- Professor Christopher Gardner
- Stanford University

Lunch Day 1: Wednesday 13th

ESTIMATED ON AVERAGE PORTION SIZES	PROTEIN (g)	PROTEIN SWAPS
Vegetable based soup (free)		
Selection of bread (dependent on portion size)	6g/slice	
Chicken Stroganoff- (soy milk- based sauce, chicken breast strips, *mushrooms, onions and gherkins (free)*	16g	1 x 2g + 2 x7g
Roasted broccoli & spring greens pasta bake- pasta, gouda, *spinach sauce, spinach, spring greens broccoli (free)*	14g	1 x 7g + 3 x 2g
Wild rice	4g	2 x 2g
New potatoes	6g	3 x 2g
Fresh fruit salad (free)		
Sandwich options		
SANDWICH FILLING	(INCL 8g BREAD)	(INCL 4 X 2g BREAD)
Roasted red pepper (free) & houmous	11g	5 x 2 g
Falafel *& beetroot (free)*	15g	1 x 7g + 4 x 2g
Turkey	15g	1 x 7g + 4 x 2g
Avocado & roasted tomato (free)	8g	4 x 2g
Sweet treats		
Overnight oats made with oat milk	6g	3 x 2g
Apple crumble with custard made *from coconut milk*	3g	1 x 2g
Fresh fruit salad (free)		
Cereal bars	3g	1 x 2g

Dinner Day 1: 13th Nov

ESIMATED ON AVERAGE PORTION SIZES	PROTEIN (g)	PROTEIN SWAPS
Starter Trio of houmous with warm flat bread & roasted butternut squash (free) (VEGAN)	7g	3 x 2g
Main course		
- Main option 1 Butterflied chargrilled chicken breast, new potatoes, roasted mediterranean vegetables (free)	65g	9 x 7g + 2 x 2g
- Main option 2 Cauliflower burger (free) with roasted sweet potato & spring vegetables (free) Vegan and gluten free option, (VE) (GFA)	3g	1 x 2g
Dessert Chocolate orange mousse with coconut milk (VE) (GF)	1-2g	1 x 2g

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Lunch Day 2: 14th November

ESTIMATED ON AVERAGE PORTION SIZES	PROTEIN (g)	PROTEIN SWAPS
Mushroom & spinach risotto: 10g (5 x 2g swaps)	10g	5 x 2g
Five bean chilli con carne and rice	14g	1 x 7g + 2 x 2g
Grilled pineapple & cinnamon with natural yogurt (free)	6g	3 x 2g
Sandwich Options		
SANDWICH FILLING	(INCL 8g BREAD)	(INCL 4 X 2g BREAD)
Roasted red pepper (free) & houmous	11g	5 x 2 g
Falafel & *beetroot (free)*	15g	1 x 7g + 4 x 2g
Turkey	15g	1 x 7g + 4 x 2g
Avocado & roasted tomato (free)	8g	4 x 2g
Sweet Treats		
Overnight oats made with oat milk	6g	3 x 2g
Apple crumble with custard made from *coconut milk*	3g	1 x 2g
Fresh fruit	Free	Free
Cereal bar	3g	1 x 2g

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Questions

Group photo before lunch

Introducing Mindfulness-based approaches to Chronic Health Conditions (part 1)

Steve Smith - Mindfulness Programmes Lead, Rare Minds

Coffee break + exhibition

Introducing Mindfulness-based approaches to Chronic Health Conditions (part 2)

Steve Smith - Mindfulness Programmes Lead, Rare Minds

November 2024

Experience of Dendrite Registries Helping Rare Disease Patients

Martin Twycross

martin.twycross@e-dendrite.com

BSc Eng., MBA

Agenda

Dendrite & Credentials

What is a Registry?
What can it do to support Rare Patients?

Examples – 3 different approaches Rare registries:

- **Our “Classic” – Clinician led**
- **Innovative – a “national support” network**
- **New – “first person” Patient led**

What makes a successful registry?

Dendrite – the company

Henley-on-Thames Head Office

25 Staff, including 14 senior prog./dev. personnel

- **Health Informatics/Clinical Data Management**
- **UK Based International Company**
- **30 year trading history**
- **Clients in 50 countries around the world**
- **Software running in 18 major languages**
- **200+ National/International Registries delivered**
- ***Rapid Development* Web Registry Platform**
- **Integrated PROs, Data Analysis & Reporting**

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Dendrite & Credentials

Dendrite – providing registries for over 30 years

Powers over 200 registries worldwide, in example:

Society of Cardiothoracic Surgery of Great Britain & Ireland

British Orthopaedic Association & NHSI

IFSO Global Bariatric Surgery Registry

New Zealand Breast Cancer Registry

British Society of Allergy & Clinical Immunology

UK Paediatric Difficult Asthma Registry

SHOT (Serious Hazards of Transfusion Registry)

British Association of Paediatric Surgeons

GARFIELD – Global Atrial Fibrillation Registry

The Robert Gregory National ARU Centre

Liverpool University Hospitals NHS Foundation Trust

What is a Registry? A *Database!*

Clinical registry: The collection of **observational clinical data** (ideally longitudinal) for a defined patient population where a **specific disease or condition is studied.**

The role of a Registry in Rare Diseases ……

…… to capture data on **real-world** activity to:

- *Close support a Patient Group/Society*
  understanding *YOUR* disease & improve QoL/ Patient Outcomes

- **to combine and make visible a small number of cases**
- **often where clinical trials are unsuitable** or impractical
- to inform and **improve clinical practice & outcomes**
- regulatory/compliance requirements
  or inform a Commissioning Body's choices, e.g.
  - MHRA, NICE
  - NHS Commissioning or Rare Diseases Advisory Group (RDAG)

A Rare Disease Registry

Collects detailed information on EVERY patient:

- ✓ Demographic data
- ✓ Detailed history and investigation
- ✓ Detailed co-existing disease info
- ✓ Detailed clinical information
- ✓ Course(s) of treatment(s)
- ✓ Unlimited follow-up data
- ✓ **PROMs** (Patient Recorded Outcome Measures)

Automated PROMs (Patient Reported Outcome Measures)

A *game-changer* in patient data collection

PROMs allows simple collection of huge amounts of patient outcome and quality of life (QoL) data.

Examples of registries using PROMs:

WMUK The Rory Morrison Waldenström's Macroglobulinaemia UK Clinical Data Registry

HADS Anxiety & EORTC

BAPRAS UK Flap Registry

Breast-Q & Enneking

bsaci improving allergy care

Juniper & Allergy Quality of Life

Secure and easy to use

High patient response rate

Multilingual

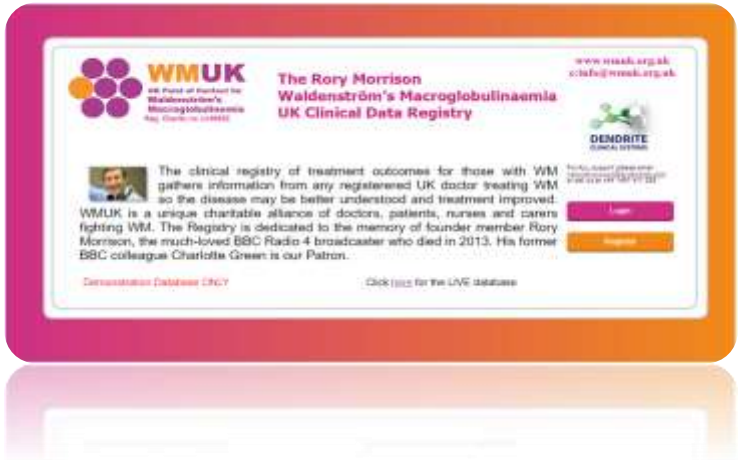
Eliminates/ reduces bias

Huge capacity for outcome /QoL data

WM - a “Classic” Clinical Registry

Waldenstrom Macroglobulinemia: a “blood cancer”

In WM white blood cells undergo changes that turn them into cancer cells



Founded by bequest - running since 2016

Set up by Leading WM Clinicians interacting with PAG

Currently 1640 recorded Patients

1st Report in 2018 – altered disease profile!

PROMs returns - 73%

Now in 3rd phase/iteration

Financially supported by

janssen | Johnson & Johnson

BeiGene

WM - a “Classic” Clinical Registry

Initially, no standard first-line treatment for WM patients; in the Registry though 2 therapies were popular options - outcomes tracked by Registry

2017 Ibrutinib (Imbruvica, Janssen) approved by NHS Cancer Drugs fund as 2nd line treatment of choice for WM,
- Registry shows 70% of patients respond well

Continuing Aims –

*“….. **as commercial partners seek to gain** approval for their (new) therapies within the NHS. We hope that it (the registry) will help to ensure commissioning bodies such as NICE are **better equipped in their decision-making processes** as they **appraise promising new therapies**”.*

CDN – an Innovative “Support Network” Registry

CDNUK
Castleman Disease Network UK

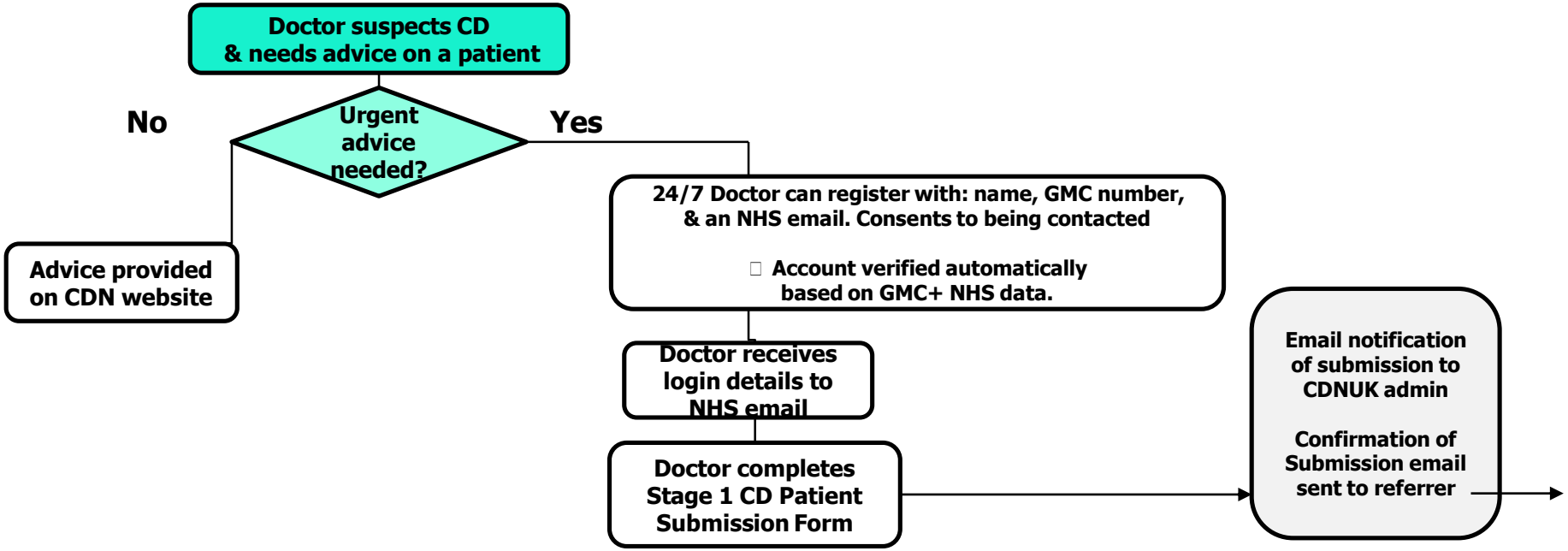
Castleman Disease: a group of rare lympho-proliferative disorders
- involving enlarged lymph nodes, with broad range of inflammatory symptoms.

Unknown if Castleman is an autoimmune disease, a cancer, or infectious disease

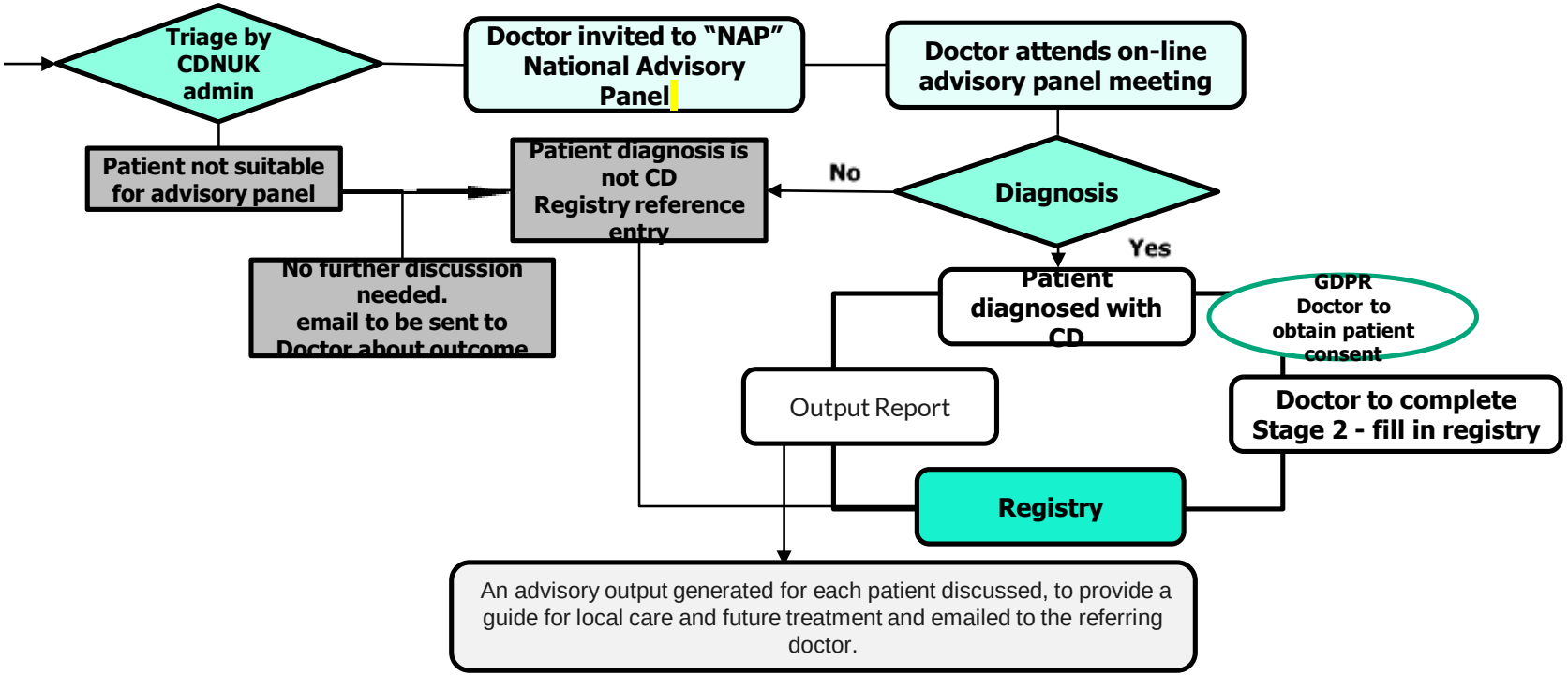
CD Network set up by leading UK Haematologist, with 4 national haem-oncologists

Started in 2023, with “seed funding” by a Pharma company

CDN – an Innovative "Support Network" Registry



CDN – an Innovative “Support Network” Registry



CDN – an Innovative "Support Network" Registry

Outcome?

***SUCCESS*! – Enables consistent diagnosis & discussion of CD patients at National level**

45 confirmed CD patients, 5 patients /month being submitted, often 1 ITU case

Monthly case review calls, with individual's outcomes review
– improved general understanding and specific treatment recommendations/outcomes

Initial observations:

CD – is perhaps a bit rarer than they thought? Or ……. Undiagnosed? Unaware?

iMCD bias? more idiopathic MCD (multicentric CD) in presenting patients
Resource implications – the most demanding form of CD presentation for managing

The AKU Registry – a new/novel Patient led Registry

Alkaptonuria; or Black Bone Disease, an extremely rare (>100 in UK) genetic condition.

AKU stops the body breaking down a chemical - *homogentisic acid*. HGA build up in body and leads to black and brittle bones and cartilage, with early onset osteoarthritis.

Using Orfadin® (Nitisinone - originally a pesticide) supports remission of this process

The **AKU Registry** is designed as a **Patient led journal**

Providing a first-person perspective of how this multi-system disease develops over time.

The AKU Registry – a new/novel Patient led Registry

The AKU registry started & developed during 2023

The registry launched in April 2024. In just 6 months .....!

Patients registered, by country

Country	Patient Count
USA	14
UK	11
India	6
Netherlands	4
Australia	3
Belgium	2
Brazil	2
Canada	2
Egypt	2
France	2
Croatia	2
Lebanon	2
UAE	1
Argentina	1
Colombia	1
Czech Republic	1
Spain	1
Greece	1
Nepal	1
New Zealand	1
Oman	1
Poland	1
Saudi Arabia	1
Slovakia	1
Sweden	1
Turkey	1
Total (26)	**66**

Patients who have made one or more journal entries,

by country

Country	Patient Count
UK	5
USA	4
Australia	3
France	2
Croatia	2
India	2
Argentina	1
Belgium	1
Brazil	1
Canada	1
Czech Republic	1
Egypt	1
Lebanon	1
Netherlands	1
Nepal	1
Poland	1
Sweden	1
Turkey	1
Total (18)	**30**

- ✓ It must be <u>set up with clear, explicit objectives</u>
- ✓ Data fields set up to support the objective
- ✓ It must be <u>easy to use</u>
- ✓ Complete, accurate input data
- ✓ Cover a good representation of patients/condition
- ✓ High quality output – credible results, useful reports
- ✓ (ensure GDPR matters covered)

Ultimately leads to **improved clinical practice** and **better outcomes for patients.**

Thank you!

Please contact me for any further questions or information.

martin.twycross@e-dendrite.com

Martin Twycross

“ Without data….. you’re just another person with an opinion.”

W. Edwards Deming

Summary + Close with Nick Sireau,CEO & Chair of Trustees AKU Society

Thank you for attending, and we look forward to seeing you for dinner this evening.

Please join us at the function bar for a drink at 7:15pm, with dinner to be served at 7:45pm.

Please remember to hand in your name badges at the registration desk on your way out, so we can re-use these for registration tomorrow morning.