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Purpose **Led,** Data **Driven.**

Bridging the Divide

How Academia/Industry collaborations have the power to transform clinical development

Professor Jennifer Visser-Rogers

PSI Conference Keynote

10th June 2025

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The year is 2007…

- PhD, supervised by Prof Jane Hutton, University of Warwick
- Focused on epilepsy

- Antiepileptic drugs (AEDs) come with side effects
- Are AEDs necessary in early epilepsy?
- Does seizure type have an effect on the risk of future seizures?

MESS

- MRC Multicentre trial for Early epilepsy and Single Seizures
- Randomised 1,443 patients to either immediate or deferred treatment
- Eligibility criteria: had at least one seizure and uncertainty about whether to proceed with treatment
- Outcomes of interest: time to first seizure, time to second seizure

MESS

Articles

Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial

Lois G Kim, Tony L Johnson, Anthony G Marson, David W Chadwick on behalf of the MRC MESS Study group

Summary

Background The MRC Multicentre trial for Early Epilepsy and Single Seizures (MESS) showed a reduced risk of further seizures in patients, for whom treatment with antiepileptic drugs was uncertain, who were randomly assigned immediate treatment compared with delayed treatment. However, there was no evidence of long-term remission rates. This study was undertaken to assess the role of patient characteristics and treatment in the prediction of seizure recurrence. This will enable decision-making on the basis of the perceived risk of treatment compared with the benefit of reducing the risk of further seizures in the initial years after diagnosis.

Methods A prognostic model was developed based on individual patient data from MESS to enable identification of patients at low, medium, or high risk of seizure recurrence. A split-sample approach was used in which the model was developed on a subsample of the full data and validated on the remainder of the sample. Distinction of the prognostic groups and predictive accuracy of the model were assessed.

Findings Number of seizures of all types at presentation, presence of a neurological disorder, and an abnormal electroencephalogram (EEG) were significant factors in indicating future seizures. Individuals with two or three seizures, a neurological disorder, or an abnormal EEG were identified as the medium-risk group, those with two of these features or more than three seizures as the high-risk group, and those with a single seizure only as the low-risk group.

Lancet Neurol 2006; 5: 317–22

Published Online March 6, 2006

DOI:10.1016/S1474-4422(06)70383-0

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"Showed a reduced risk of further seizures, for whom treatment with antiepileptic drugs was uncertain, who were randomly assigned immediate treatment compared with delayed treatment. However, there was no evidence of long-term remission rates"

MESS

Data arrives in two parts:

- Pre-randomisation event count, X_i – the number of seizures an individual has experienced in a given period of time prior to entry to the trial
- Post-randomisation survival times, (Y_{1i}, Y_{2i}) – following randomisation to treatment policy, times to first and second seizure are measured for each individual

Standard analysis treated the event count as a covariate when analysing times to event

Joint Modelling – Poisson Process

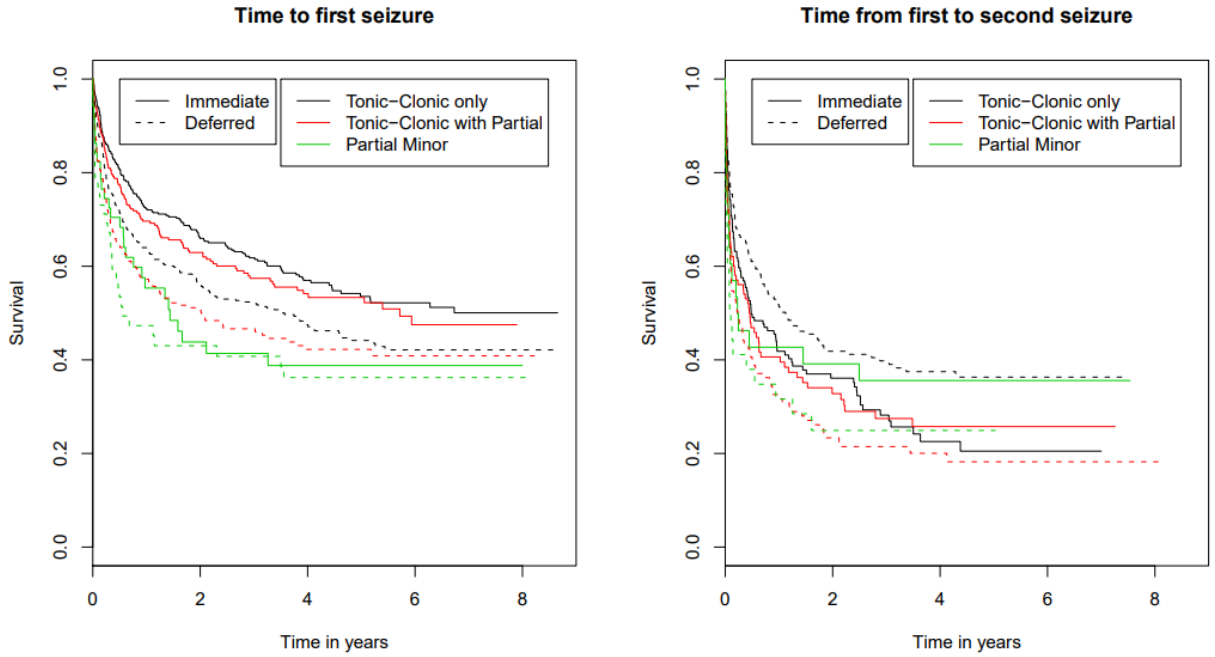
Joint model specified by the following equations:

$$
\begin{aligned}
f_{X|\nu}(x_i \mid \nu_i; \lambda_i, u_i) &= \frac{(\lambda_i u_i \nu_i)^{x_i} \exp(-\lambda_i u_i \nu_i)}{x_i!} \\
f_{Y_j|\nu}(y_{ji} \mid \nu_i; \lambda_i, \psi_i) &= \lambda_i \psi_i \nu_i \exp(-\lambda_i \psi_i \nu_i y_{ji}),\ j = 1, 2 \\
g_\nu(\nu_i; \alpha) &= \frac{\alpha^\alpha \nu_i^{\alpha-1} \exp(-\alpha \nu_i)}{\Gamma(\alpha)}
\end{aligned}
$$

$$
\lambda_i = \exp(\beta_1' \boldsymbol{z}_{1i}) \text{ and } \psi_i = \exp(\beta_2' \boldsymbol{z}_{2i})
$$

But…

- On average, 50% of people do not experience a recurrence after a single seizure
- Risk of future seizures increases with the number of previous seizures



Cure Fractions

Large proportion of individuals ‘immune’ from seizures

$$
\begin{aligned}
f_{X|\nu}(x_i \mid \nu_i; \lambda_i, u_i) &= \frac{(\lambda_i u_i \nu_i)^{x_i} \exp(-\lambda_i u_i \nu_i)}{x_i!} \\
f_{Y_j|\nu}(y_{ji} \mid \nu_i; \lambda_i, \psi_i, p_i) &= p_i \lambda_i \psi_i \nu_i \exp(-\lambda_i \psi_i \nu_i y_{ji}) \\
S_{Y_j|\nu}(y_{ji} \mid \nu_i; \lambda_i, \psi_i, p_i) &= 1 - p_i + p_i \exp(-\lambda_i \psi_i \nu_i y_{ji}) \\
g_\nu(\nu_i; \alpha) &= \frac{\alpha^\alpha \nu_i^{\alpha-1} \exp(-\alpha \nu_i)}{\Gamma(\alpha)}
\end{aligned}
$$

$$
\lambda_i = \exp(\beta_1' \boldsymbol{z}_{1i}),\ \psi_i = \exp(\beta_2' \boldsymbol{z}_{2i}) \text{ and } p_i = \frac{\exp(\kappa' \boldsymbol{w}_i)}{1+\exp(\kappa' \boldsymbol{w}_i)}
$$

IID Assumption

Evidence to suggest that ψ_{iy} change through time

$$
\begin{aligned}
f_{X|\nu}(x_i \mid \nu_i; \lambda_i, u_i) &= \frac{(\lambda_i u_i \nu_i)^{x_i} \exp(-\lambda_i u_i \nu_i)}{x_i!} \\
f_{Y_1|\nu}(y_{1i} \mid \nu_i; \lambda_i, \psi_{1i}) &= \lambda_i \psi_{1i} \nu_i \exp(-\lambda_i \psi_{1i} \nu_i y_{1i}) \\
f_{Y_2|\nu}(y_{2i} \mid \nu_i; \lambda_i, \psi_{1i}, \psi_{2i}) &= \lambda_i \psi_{1i} \psi_{2i} \nu_i \exp(-\lambda_i \psi_{1i} \psi_{2i} \nu_i y_{2i}) \\
g_\nu(\nu_i; \alpha) &= \frac{\alpha^\alpha \nu_i^{\alpha-1} \exp(-\alpha \nu_i)}{\Gamma(\alpha)}
\end{aligned}
$$

$\lambda_i = \exp(\beta_1' \boldsymbol{z}_{1i})$, $\psi_{1i} = \exp(\beta_2' \boldsymbol{z}_{2i})$ and $\psi_{2i} = \exp(\beta_3' \boldsymbol{z}_{3i})$

Results

- Complex models were able to pick up interactions that standard analyses couldn’t
- Those with partial seizures had a cure rate of around 30%, compared with a cure rate of 50% for tonic-clonic
- No treatment effect on cure rate or seizure rate for a normal EEG, but immediate treatment had higher cure rates and bigger reductions in seizures for those with an abnormal EEG
- For those with partial seizures, treatment didn’t have as big an effect on whether they continued to have partial seizures, but did prevent incidence of secondary tonic-clonic

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Moving into Heart Failure

Composite endpoints are the standard approach in many cardiovascular trials

- Include two or more types of related clinical events
- Increase the event rate and avoid multiplicity
- Analysis focused on time to first event

- Examples in cardiovascular trials
  - CV death, MI, and stroke in hypertension trials
  - CV death and HF hospitalisation in heart failure trials

What is Wrong with Composite Endpoints?

Only the first occurring endpoint is analysed

- HF not characterised by a single event
- Chronic diseases characterised by recurrent events
- Repeat, nonfatal events ignored

Recurrent Event Methodology

- Non-parametric estimator for mean cumulative function

- Time-to-event approaches
  - WLW: cumulative time from randomisation to events
  - PWP: analyses gap times, conditional risk sets
  - Andersen-Gill: extension of Cox proportional-hazards model

- Methods based on event rates
  - Poisson: total # events divided by follow-up
  - Negative Binomial: individual Poisson rates which vary according to a Gamma

Scientific Questions

- Does the intervention decrease the event number over the study period compared to control?
- How many events does the intervention prevent, on average, compared to the control?
- What is the intervention effect on the number of higher-order events, e.g. 3rd event, compared to control?
- What is the effect of the intervention on the times to subsequent events among those who experienced a preceding event?

- Which aspect of the recurrent event process is of interest?
- Which methods will allow us to accurately measure the true burden of disease on patients?

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Statistical Considerations

- Modelling framework
  - Parametric/semi-parametric/non-parametric
- Event rate
  - Constant/time-varying/unspecified
- Overdispersion

- Complexity of methodology
- Experience in regulatory assessment
- Gold standard methodology in indications

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Incorporating CV Death

- One way to reduce the number of hospitalisations is for patients to die
- Increase in HF hospitalisations associated with increased risk of death
- Censoring due to CV death is not independent of hospitalisations

I’ve got just the solution!

Joint Modelling

- Joint modelling of longitudinal data and survival times well established
- What if I could use what I've done on event counts and survival times in a similar way?

Joint Frailty Model

- Each patient has their own independent frailty term, ω_i
- Proportionately affects heart failure hospitalisation rate and time to death
- Integrate out random effects to jointly model two event processes

Likelihood

Δ_i indicator for death

$$L_i = \int_{\omega_i} f_i(n_i \mid \omega_i) \left[f_i(x_i \mid \omega_i) \right]^{\Delta_i} \left[S_i(x_i \mid \omega_i) \right]^{1-\Delta_i} f_i(\omega_i) d\omega_i$$

Likelihood

$N_i \mid \omega_i \sim \text{Poisson}\ (\varphi_i x_i \omega_i)$

$$L_i = \int_{\omega_i} f_i(n_i \mid \omega_i) \left[f_i(x_i \mid \omega_i) \right]^{\Delta_i} \left[S_i(x_i \mid \omega_i) \right]^{1-\Delta_i} f_i(\omega_i) d\omega_i$$

Likelihood

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$$L_i = \int_{\omega_i} \frac{(\varphi_i x_i \omega_i)^{n_i} \exp(\varphi_i x_i \omega_i)}{n_i!} \left[f_i(x_i \mid \omega_i)\right]^{\Delta_i} \left[S_i(x_i \mid \omega_i)\right]^{1-\Delta_i} \times f_i(\omega_i) d\omega_i$$

Likelihood

$X_i \mid \omega_i \sim \text{Exponential}\ (\gamma_i \omega_i)$

$$L_i = \int_{\omega_i} \frac{(\varphi_i x_i \omega_i)^{n_i} \exp(\varphi_i x_i \omega_i)}{n_i!} \left[f_i(x_i \mid \omega_i)\right]^{\Delta_i} \left[S_i(x_i \mid \omega_i)\right]^{1-\Delta_i} \times f_i(\omega_i) d\omega_i$$

Likelihood

$$X_i \mid \omega_i \sim \text{Exponential}\ (\gamma_i \omega_i)$$

$$L_i = \int_{\omega_i} \frac{(\varphi_i x_i \omega_i)^{n_i} \exp(\varphi_i x_i \omega_i)}{n_i!} \left[(\gamma_i \omega_i) \exp(-\gamma_i x_i \omega_i)\right]^{\Delta_i} \left[\exp(-\gamma_i x_i \omega_i)\right]^{1-\Delta_i} \times f_i(\omega_i) d\omega_i$$

Likelihood

$\omega_i \sim \text{Gamma}\ (\theta, \theta)$

$$L_i = \int_{\omega_i} \frac{(\varphi_i x_i \omega_i)^{n_i} \exp(\varphi_i x_i \omega_i)}{n_i!} \left[(\gamma_i \omega_i) \exp(-\gamma_i x_i \omega_i)\right]^{\Delta_i} \left[\exp(-\gamma_i x_i \omega_i)\right]^{1-\Delta_i} \times f_i(\omega_i) d\omega_i$$

Likelihood

$\omega_i \sim$Gamma (θ, θ)

$$L_i = \int_{\omega_i} \frac{(\varphi_i x_i \omega_i)^{n_i} \exp(\varphi_i x_i \omega_i)}{n_i!} \left[(\gamma_i \omega_i) \exp(-\gamma_i x_i \omega_i)\right]^{\Delta_i} \left[\exp(-\gamma_i x_i \omega_i)\right]^{1-\Delta_i}$$
$$\times \frac{1/\theta^{1/\theta}}{\Gamma(1/\theta)} \omega_i^{1/\theta - 1} \exp\left(-\frac{\omega_i}{\theta}\right) d\omega_i$$

Likelihood

$$L_i = \int_{\omega_i} \frac{(\varphi_i x_i \omega_i)_i^n \exp(\varphi_i x_i \omega_i)}{n_i!} \left[(\gamma_i \omega_i) \exp(-\gamma_i x_i \omega_i)\right]^{\Delta_i} \left[\exp(-\gamma_i x_i \omega_i)\right]^{1-\Delta_i} \times \frac{(1/\theta)^{1/\theta}}{\Gamma(1/\theta)} \omega_i^{1/\theta - 1} \exp\left(-\frac{\omega_i}{\theta}\right) d\omega_i$$

- Integral has closed form
- Maximisation is straightforward using Newton-Raphson

Semi-Parametric JFM

- Can remove distributional assumptions on hospitalisation and death rates
- And relax the common frailty assumption

$$
\begin{aligned}
r_i(t|\omega_i) &= \omega_i \varphi_i r_0(t) = \omega_i r_i(t) \\
h_i(t|\omega) &= \omega_i^{\alpha} \gamma_i h_0(t) = \omega_i^{\alpha} h_i(t)
\end{aligned}
$$

Regulatory Approval

- Composite of total (first and repeat) HF hospitalisations and CV death

- One single endpoint, compared with JFM
- Natural extension from composite of first HF hospitalisation and CV death

Composite Endpoints

- Assumes treatment has a similar direction and magnitude of effect on all components
- Components are of similar importance to patients and clinicians

- HF hospitalisations dominate composite endpoint
- Critically important to report individual component outcomes alongside the composite

I wasn’t prepared for the types of questions industry and regulators were going to ask…

…they approached the problem in a very different way to me

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Commercial Input to Enrich Science

PLOS MEDICINE

OPEN ACCESS Freely available online

The PLoS Medicine Debate

In Global Health Research, Is It Legitimate To Stop Clinical Trials Early on Account of Their Opportunity Costs?

James V. Lavery[1,2,3*], Peter A. Singer[3], Renee Ridzon[4], Jerome A. Singh[2,3,5], Arthur S. Slutsky[6,7], Joseph J. Anisko[8], David Buchanan[9*]

1 Centre for Research on Inner City Health and Centre for Global Health Research, The Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada, 2 Dalla Lana School of Public Health and University of Toronto, Toronto, Ontario, Canada, 3 McLaughlin-Rotman Centre for Global Health, University Health Network and Joint Centre for Bioethics, University of Toronto, Toronto, Ontario, Canada, 4 HIV, TB & Reproductive Health Program, Bill & Melinda Gates Foundation, Seattle, Washington, United States of America, 5 Centre for the AIDS Programme of Research in South Africa (CAPRISA), Durban, KwaZulu-Natal, South Africa, 6 Departments of Medicine and Critical Care, and The Keenan Research Centre in the Li Ka Shing Knowledge2 Institute of St. Michael's Hospital, Toronto, Ontario, Canada, 7 Departments of Medicine, Surgery and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada, 8 Independent Consultant, West Chester, Pennsylvania, United States of America, 9 School of Public Health and Health Sciences, University of Massachusetts, Amherst, Massachusetts, United States of America

Background to the debate: After the failure of three large clinical trials of vaginal microbicides, a *Nature* editorial stated that the microbicide field "requires a mechanism to help it make rational choices about the best candidates to move through trials" [1]. In this month's debate, James Lavery and colleagues propose a new mechanism, based on stopping trials early for "opportunity costs." They argue that microbicide trial sites could have been saturated with trials of scientifically less advanced products, while newer, and potentially more promising, products were being developed. They propose a mechanism to relocate resources invested in existing trials of older products that might be better invested in more scientif-

series of scientific setbacks and social challenges [2,3]. Clinical trials require a large amount of financing, research and clinical infrastructure, investigator expertise and time, and goodwill and buy-in of communities from which thousands of research participants are enrolled for many years. The extent to which these resources can continue to be mobilized to meet the anticipated demand in HIV prevention trials, and other areas of global health research, is unknown.

We turned our attention to the microbicide field in October 2006. At that time, available clinical trial sites in the developing world were nearing saturation with trials of scientifically less advanced, less promising, "first generation" products (e.g., polyanion, surfactant, and buffering microbicides), while newer, potentially more promising, "next generation" anti-

was growing concern that the "cycle time" of development of next generation products would outpace the capacity for clinical trial testing, resulting in a queue for testing of antiretroviral-containing microbicides. This scenario did not come to fruition as unexpected product failures and prematurely halted trials emptied several large clinical trial sites and resolved the "microbicides queue problem," albeit in an extremely disappointing fashion. But a *Nature* editorial at the time called for a mechanism to address this problem [1].

Although the microbicides queue problem receded, it would be unwise to view it as an isolated case. With massive investments in discovery and development in global health during the past decade, promising new drugs, vaccines, and devices could emerge ready for phase III testing more rapidly than the appropriate clinical

Li et al. BMC Medical Research Methodology (2023) 23:236
https://doi.org/10.1186/s12874-023-02049-6

BMC Medical Research Methodology

RESEARCH

Open Access

Adaptive designs in critical care trials: a simulation study

W. Li[1,2*], V. Cornelius[3], S. Finfer[4,5,6], B. Venkatesh[4,5] and L. Billot[4,5]

Abstract

Background Adaptive clinical trials are growing in popularity as they are more flexible, efficient and ethical than traditional fixed designs. However, notwithstanding their increased use in assessing treatments for COVID-19, their use in critical care trials remains limited. A better understanding of the relative benefits of various adaptive designs may increase their use and interpretation.

Methods Using two large critical care trials (ADRENAL. ClinicalTrials.gov number, NCT01448109. Updated 12-12-2017; NICE-SUGAR. ClinicalTrials.gov number, NCT00220987. Updated 01-29-2009), we assessed the performance of three frequentist and two bayesian adaptive approaches. We retrospectively re-analysed the trials with one, two, four, and nine equally spaced interims. Using the original hypotheses, we conducted 10,000 simulations to derive error rates, probabilities of making an early correct and incorrect decision, expected sample size and treatment effect estimates under the null scenario (no treatment effect) and alternative scenario (a positive treatment effect). We used a logistic regression model with 90-day mortality as the outcome and the treatment arm as the covariate. The null hypothesis was tested using a two-sided significance level (α) at 0.05.

Results Across all approaches, increasing the number of interims led to a decreased expected sample size. Under the null scenario, group sequential approaches provided good control of the type-I error rate; however, the type I error rate inflation was an issue for the Bayesian approaches. The Bayesian Predictive Probability and O'Brien-Fleming approaches showed the highest probability of correctly stopping the trials (around 95%). Under the alternative scenario, the Bayesian approaches showed the highest overall probability of correctly stopping the ADRENAL trial for efficacy (around 91%), whereas the Haybittle-Peto approach achieved the greatest power for the NICE-SUGAR trial. Treatment effect estimates became increasingly underestimated as the number of interims increased.

Conclusions This study confirms the right adaptive design can reach the same conclusion as a fixed design

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We need to break down the siloes

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What can Industry Learn from Academia?

- Methodological innovation
- Patient-centred approaches
- Transparency and open science
- Focus on the scientific questions
- Creative use of limited funding

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What can Academia Learn from Industry?

- Operational efficiency and quality assurance
- Regulatory alignment
- Speed and scalability
- Participant recruitment and retention
- Commercialisation thinking

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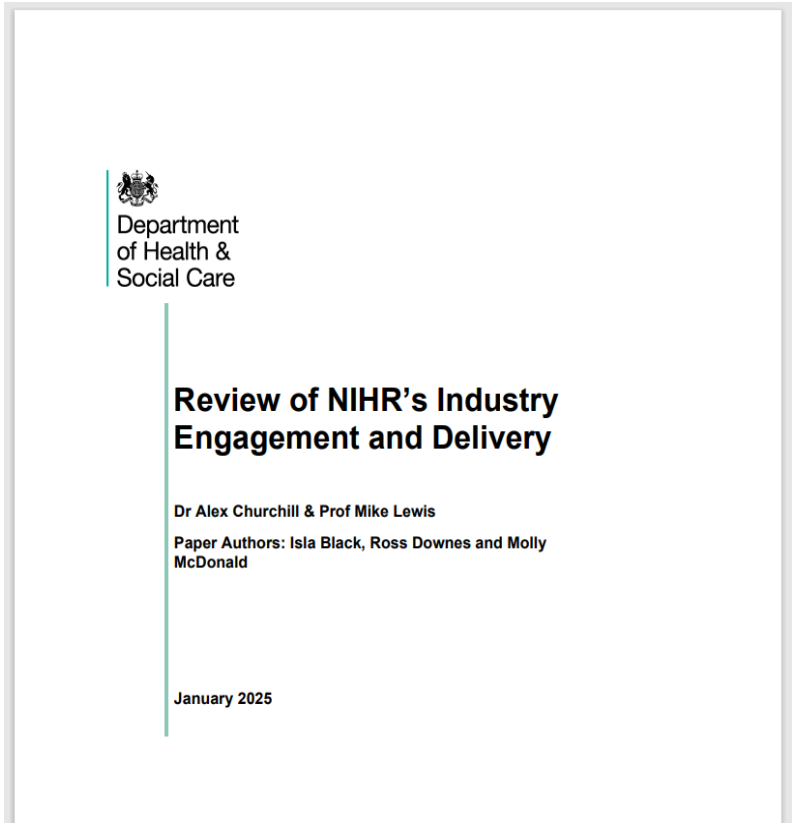
NIHR Industry Engagement Review

- Shape how NIHR engages with industry going forward
- Role of NIHR in working with industry
  - Given its wide-ranging scope, the NIHR plays a vital role in fostering collaboration between commercial and non-commercial research, recognising that both are essential to advancing healthcare innovation.
  - In order to meet the government's ambitions for the UK's life sciences sector, the NIHR needs to ensure it has consistency and efficiency in the way it engages with, and delivers for industry.

Key recommendations

1. Strengthening Internal Coordination & Leadership – Establishing an NIHR-wide Strategic Industry Engagement and Delivery Board to improve visibility, streamline support, and drive collaboration.
2. Developing a Unified Key Account Management (KAM) Approach – Co-producing a set of guiding KAM principles to ensure provision and consistency across NIHR.
3. Enhancing SME Engagement – Establishing a dedicated SME-focused working group to shape NIHR's strategy in this area.
4. Defining Industry Engagement Metrics – Introducing consistent, organisation-wide performance metrics to measure and enhance engagement and delivery.


Department of Health & Social Care

Review of NIHR's Industry Engagement and Delivery

Dr Alex Churchill & Prof Mike Lewis

Paper Authors: Isla Black, Ross Downes and Molly McDonald

January 2025

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FDA Complex Innovative Designs

- The CID Paired Meeting Program is designed to:
- Facilitate the use of CID approaches with emphasis in late-stage drug development.
- Promote innovation by allowing FDA to publicly discuss the trial designs accepted by the paired meeting program, including trial designs for medical products that have not yet been approved by FDA.

FDA Center for Clinical Trial Innovation

- FDA Center for Drug Evaluation and Research Center for Clinical Trial Innovation (C3TI) to “support innovative approaches to clinical trials designed to improve drug development efficiency through enhanced communication and collaboration”
  - Facilitate sharing of lessons learned across CDER's existing clinical trial innovation programs
  - Serve as the single CDER point of contact to support non-product-specific questions about clinical trial innovation
  - Support knowledge-sharing through discussion forums, public workshops, communications, and a knowledge repository consolidating information on CDER's clinical trial innovation efforts
  - Host a C3TI demonstration program for sponsors of innovative clinical trials in the pre-investigational new drug application ("pre-IND") or IND phase

Moving from Academia to Industry

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Why did I move?

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You're moving to the dark side

You haven't paid your dues in industry

Can we come to you when we need sponsorship

You're selling out for more money

What do you know about my job?

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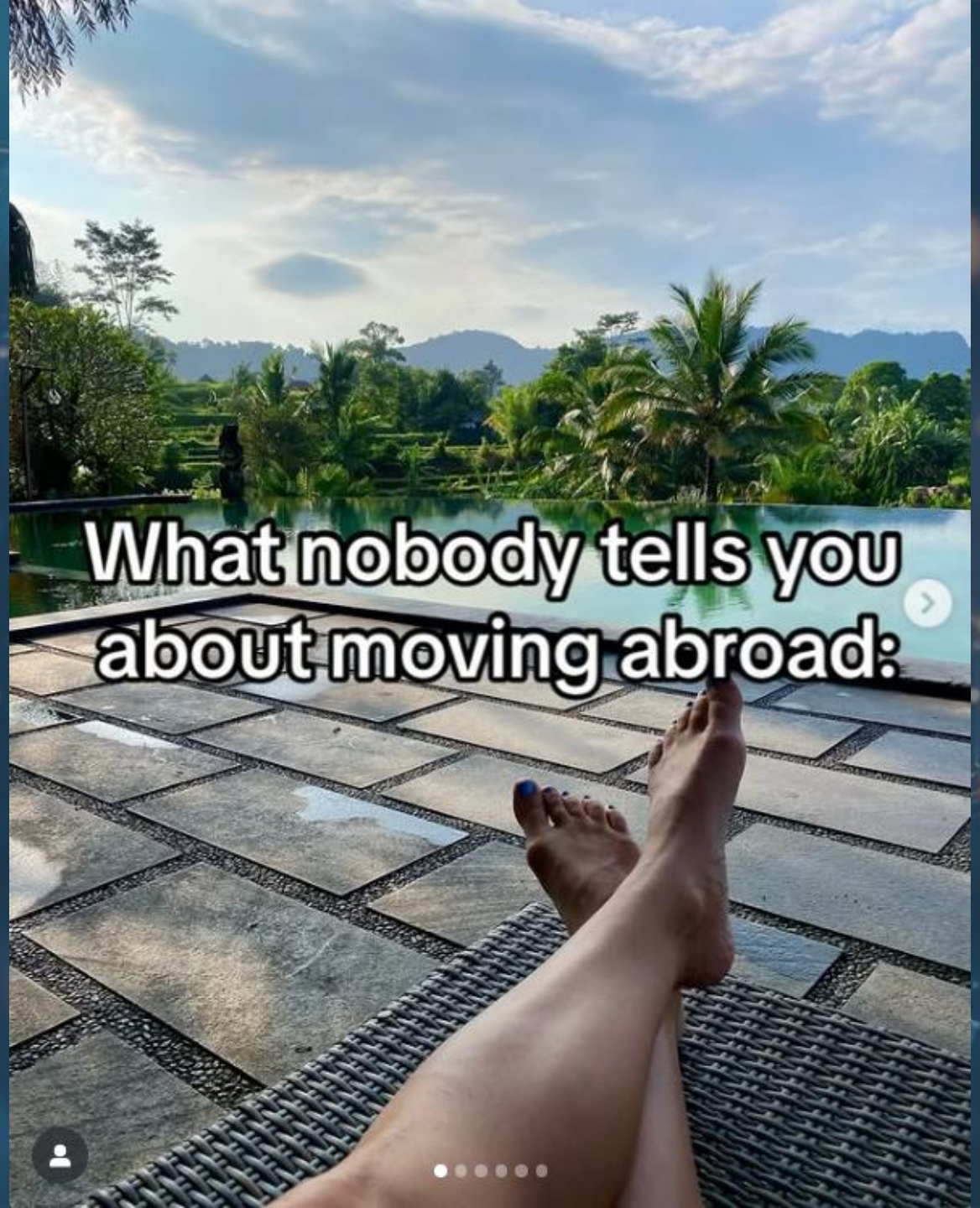

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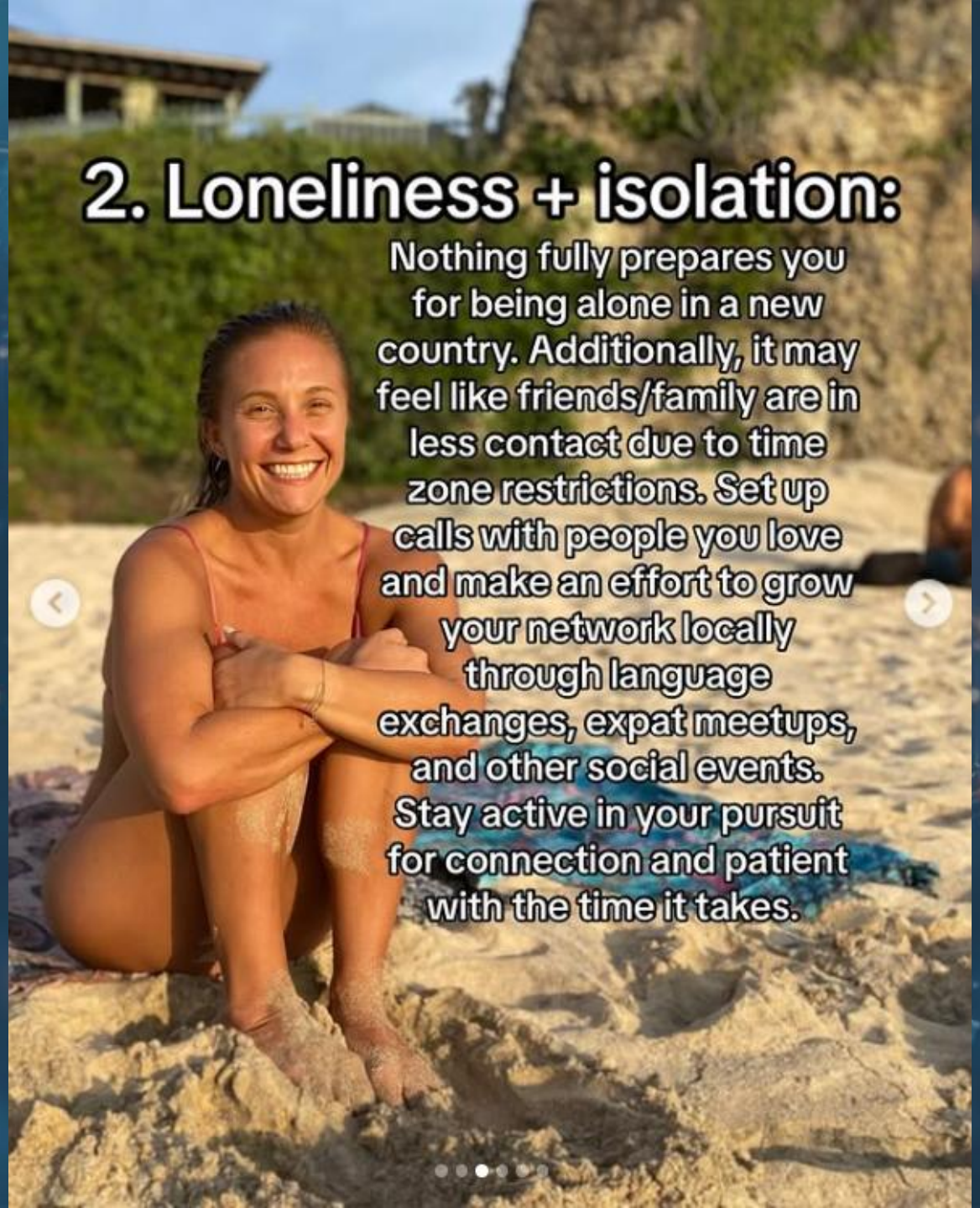

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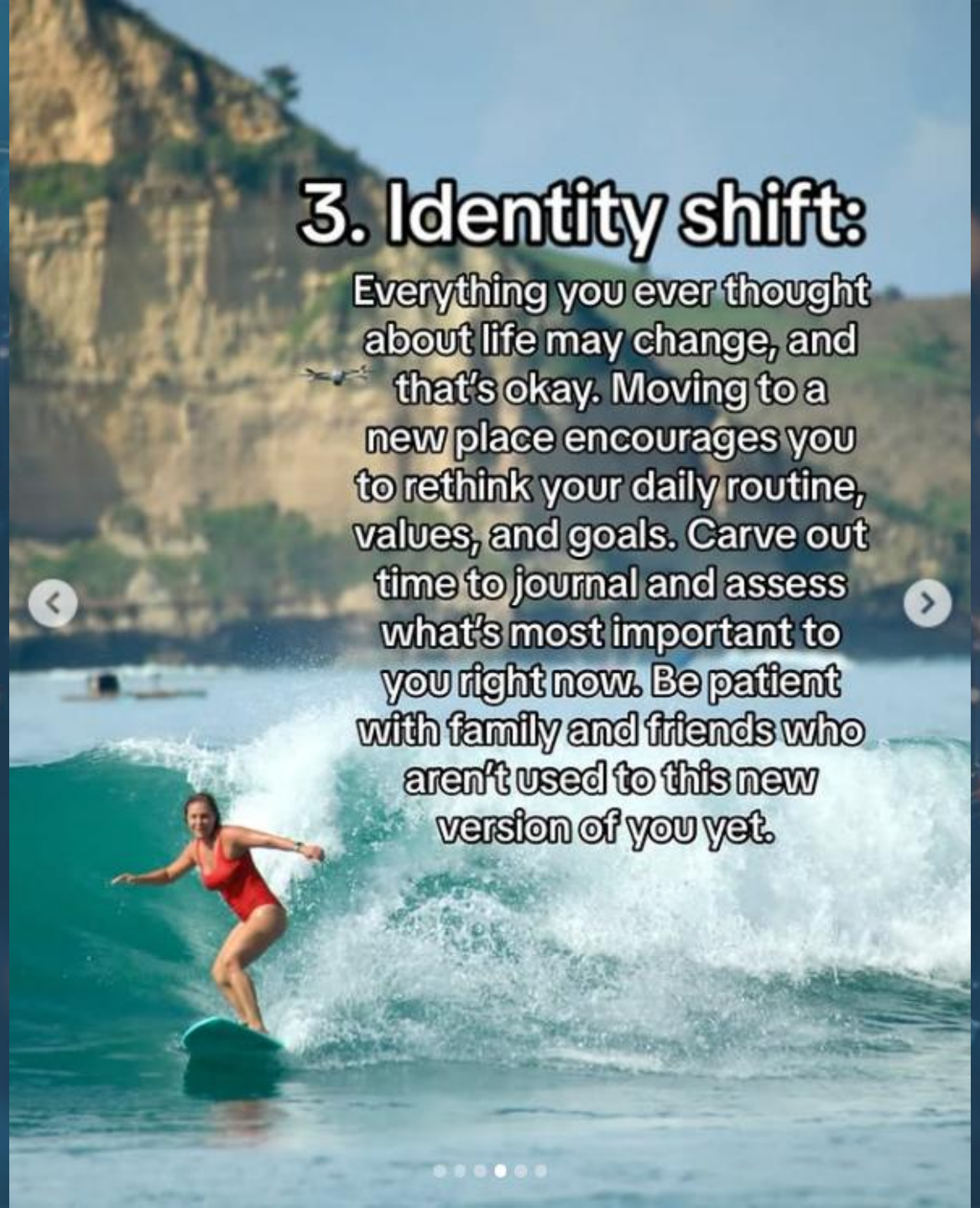

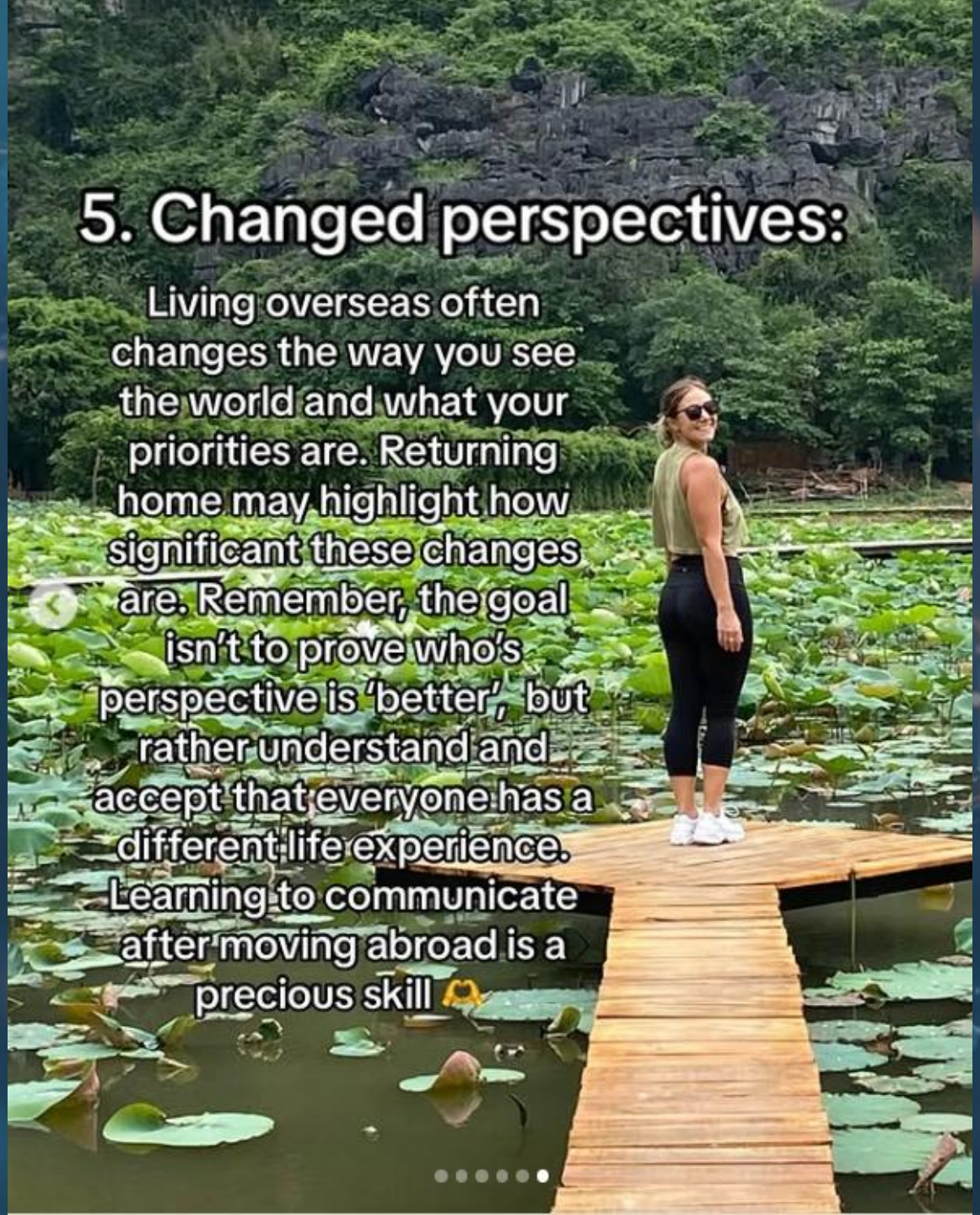

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It’s kind of like being a northerner living down south…

…you’re not really accepted in either anymore

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We’re all Clinical Trial Statisticians

- We need to break down our preconceptions
- Academic and industry statisticians bring complimentary experiences and perspectives

- Academia/industry collaborations will also be vital when thinking about the evolving role of the statistician
- How academics talk to their students about industry matters
- Dull and evil!

PSI and EFSPI

- Key questions
  - How do we change the perception of industry amongst academics?
  - Do the next gen statisticians have the skill sets needed for industry?
- Goals
  - What does good look like?
    - Curriculum/internships
    - Collaborations
  - Landscape map
  - Root cause of negative perceptions
    - Unique to statistics?

PSI and EFSPI – First Steps

Leverage existing natural connections

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Purpose **Led,** Data **Driven.**

Thank you

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