



Adaptive Designs: A Fad or the Future of Clinical Research?

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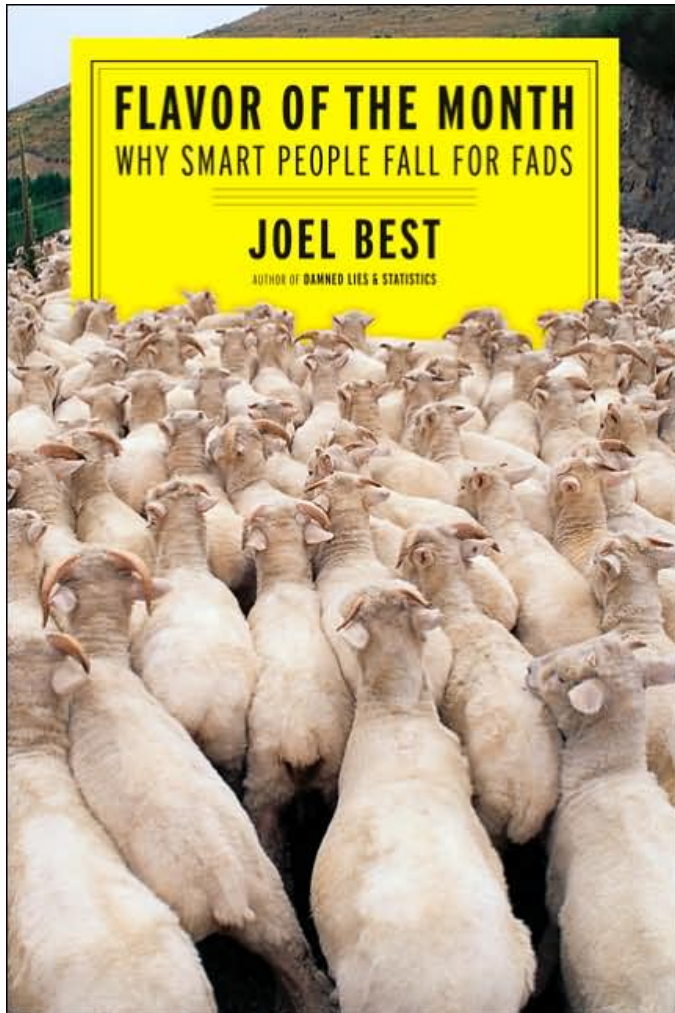
Global R&D, Sandwich, UK.

“Views presented are not necessarily those of Pfizer”

Our Charge

- discussing the concepts
 - ◆ emphasis on what is currently doable
 - ◆ what the future may hold (official soothsayers)

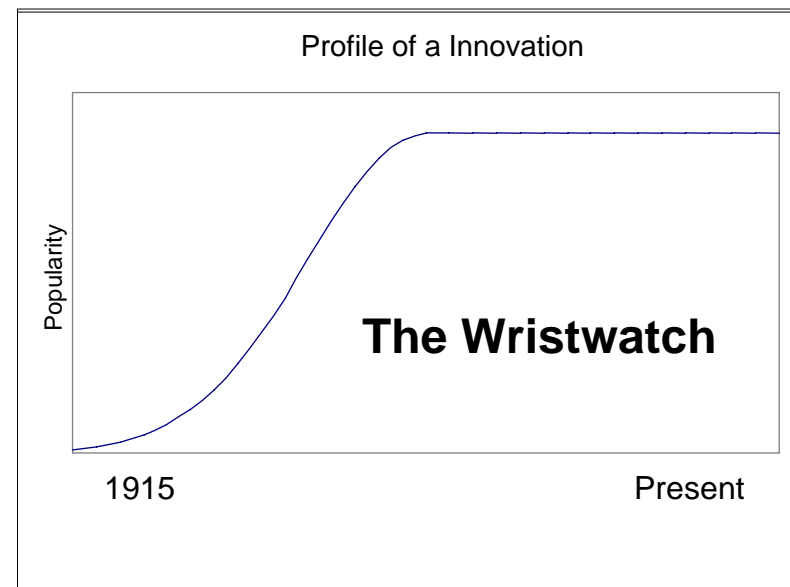
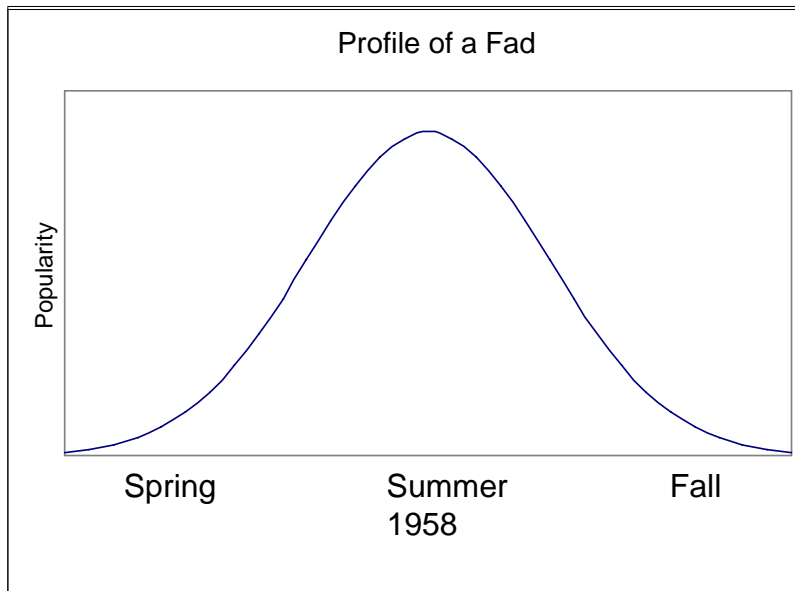
What is a Fad?



- This year's most popular Christmas Toy may be a fad
- Late 1950's – the hula-hoop was a fad

What is a Fad?

- This year's most popular Christmas Toy may be a fad
- IN 1958 – the hula-hoop was a fad



Lifecycle of a Fad

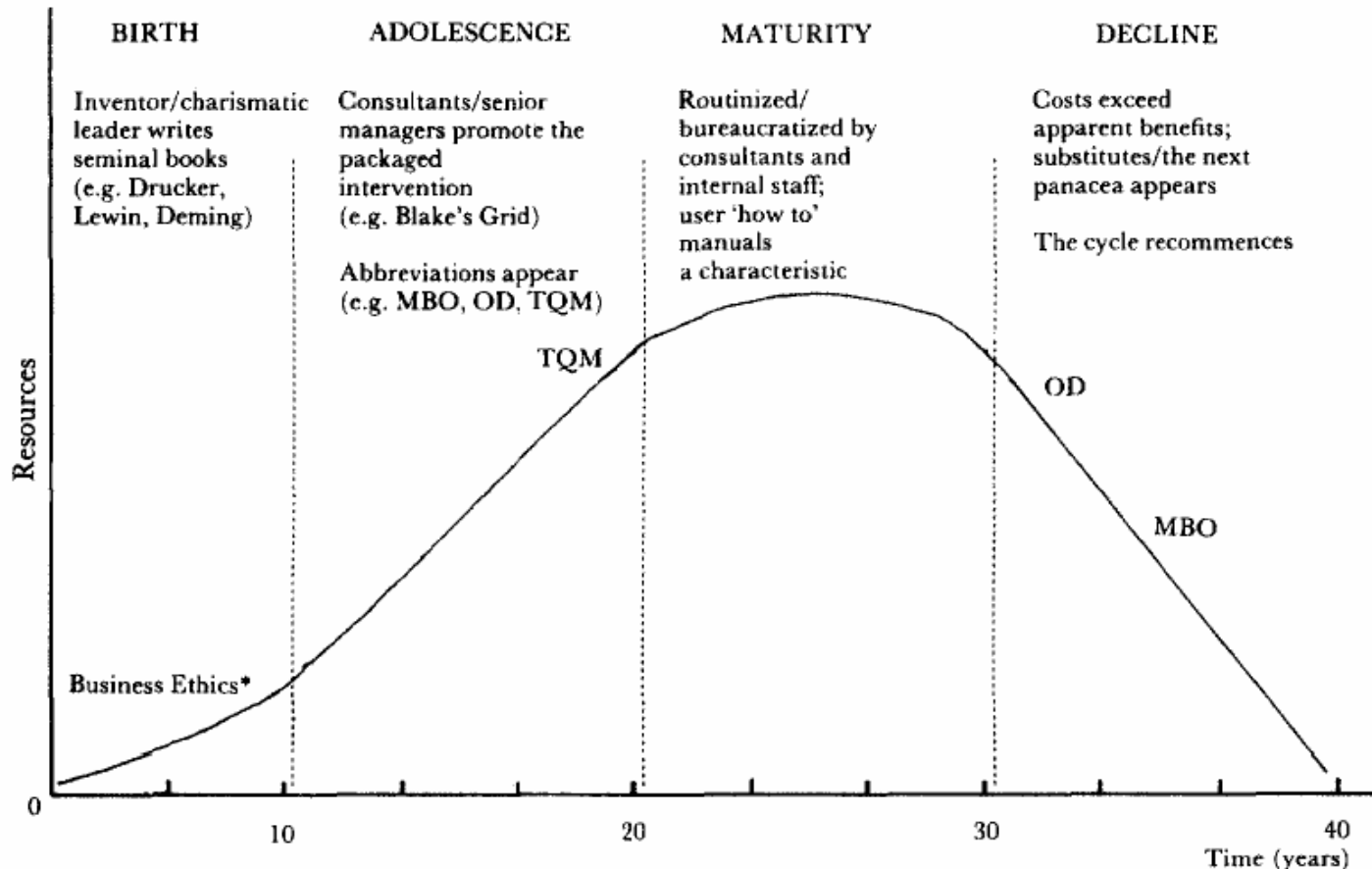
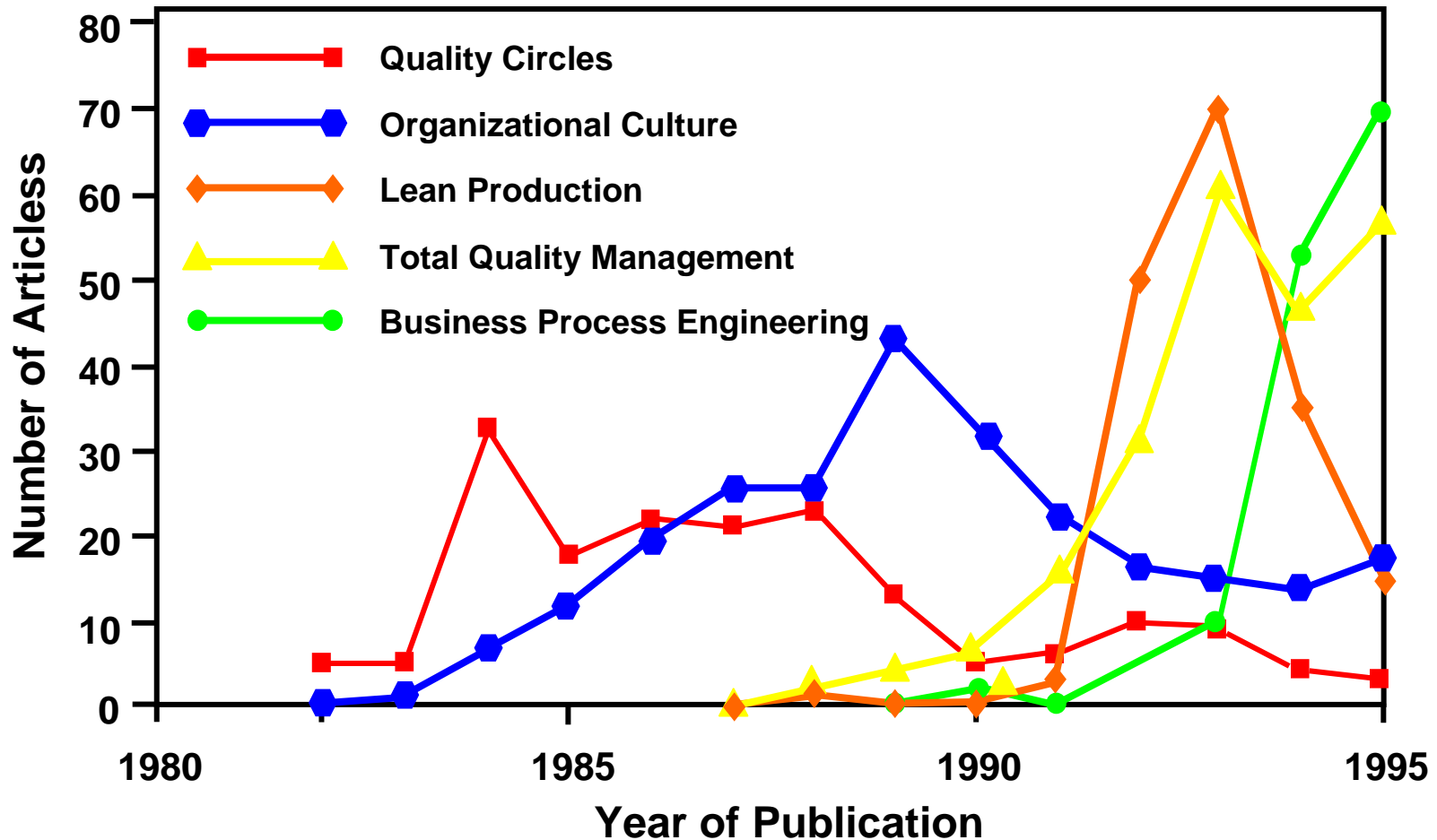


Figure 1. A speculative panacea life-cycle

*See Smith K. (1990)

Adjusted Number of Publications



A. Kieser (1997).
Rhetoric and Myth in Management Fashion
Organization, 4, 49-74

- “First to market with a new chemical entity is a good thing... first to regulation with a new [statistical] method may not be”

Adaptive Ideas Are Not New

ON THE LIKELIHOOD THAT ONE UNKNOWN PROBABILITY EXCEEDS ANOTHER IN VIEW OF THE EVIDENCE OF TWO SAMPLES.

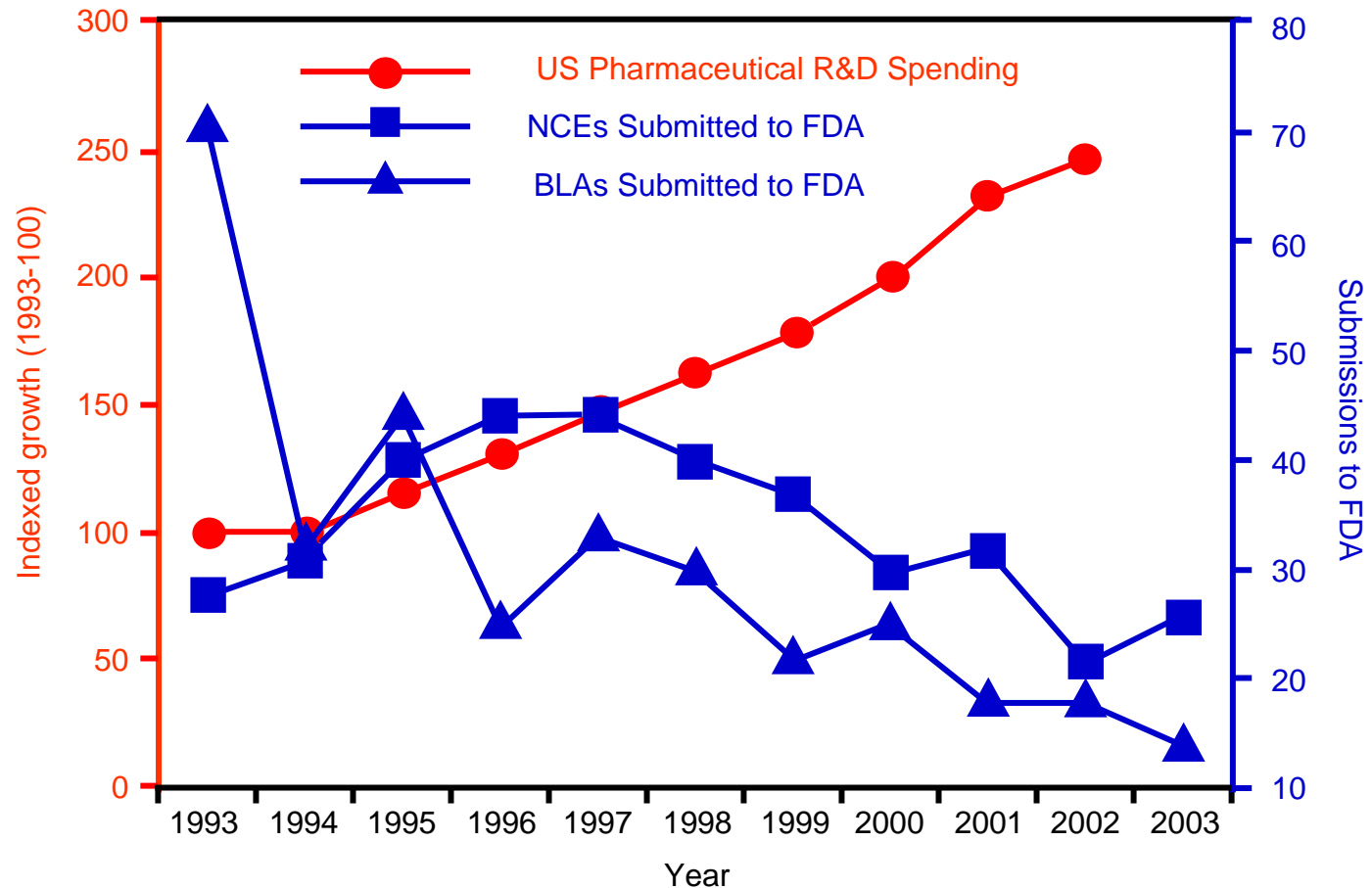
BY WILLIAM R. THOMPSON. From the Department of Pathology,
Yale University.

Biometrika, 1933

Thus, if, in this sense, P is the probability estimate that one *treatment* of a certain class of individuals is *better* than a second, as judged by data at present available, then we might take some monotone increasing function of P , say $f_{(P)}$, to fix the fraction of such individuals to be treated in the *first manner*, until more evidence may be utilised, where $0 \leq f_{(P)} \leq 1$; the remaining fraction of such individuals $(1 - f_{(P)})$ to be treated in the *second manner*; or we may establish a probability of treatment by the two methods of $f_{(P)}$ and $1 - f_{(P)}$, respectively. If

- Ethical Design – concentrating on delivering the best treatment to the most patients
- Forerunner of the Randomised Play-the-winner Design (Greg Campbell)
- Catalyst for the development of Bandit designs

Why we are here today?



Data source : PAREXEL's Pharmaceutical R&D Statistical SourceBook 2002/2003

Adaptive Phase II/Phase III Designs

■ Desire?

- ◆ Narrowing the “White Space” – Transition zone
- ◆ Change as much as feasible
 - Endpoints, statistics, doses, drop, include etc etc
- ◆ Protect the type I error

Clarity of Aims/Objectives

“The clinical trial is a carefully, and ethically, designed experiment with the aim of answering some precisely framed question”

Sir Austin Bradford Hill

Principles of Medical Statistics - 9th Ed. 1971

Objectives

- Faster
- Cheaper
- Better

Objective Creep and Optimality

- “Best” design to learn about dose-response
 - ◆ learn about an extreme aspect of dose-response – identify a single dose
 - ◆ Compare the response at that single dose to placebo
 - ◆ If the trial is positive make it “pivotal”, “confirmatory” – persuade the “regulators”



START

LEARNING

FINISH

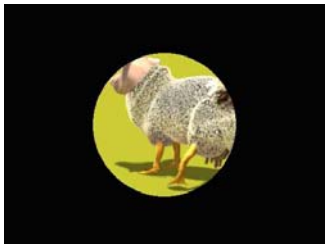


CONFIRMING

Eierlegende WollmilchSau



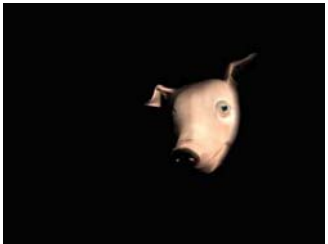
Egg-laying



Woolly-coated



Milk-giving



Pig



The late Lew Sheiner Learning and Confirming (1997)



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COMMENTARY

Learning versus confirming in clinical drug development

Lewis B. Sheiner, MD *San Francisco, Calif.*

The late Lew Sheiner Learning and Confirming (1997)

Table I. Study designs for learning and confirming

<i>Design feature</i>	<i>Confirming</i>	<i>Learning</i>
<i>Assignment</i>		
Randomized assignment	Yes	Yes
Regimens	Few	Many
Subjects	Homogeneous	Heterogeneous
Balance	Yes	Optional
<i>Observation</i>		
Balance	Yes	Optional
<i>Prognostic</i>		
Baseline	Few	Many
Ongoing	None	Many
<i>Exposure</i>		
Compliance	No	Yes
Pharmacokinetics	No	Yes
<i>Outcome</i>		
Clinical	Few	Many
Pharmacologic	Very few	Many
<i>Analysis</i>		
View	Frequentist Testing	Bayesian Estimation
Assumptions	Few	Many
Certainty	Great	Little
Model for outcome	Simple null	Causal
Treatment	As-assigned	As-treated
Prognostic variables	Stratify	Model

- What seems to be missing is
 - ◆ Any notion of model-based drug development
 - ◆ What we learn from pre-clinical information
 - ◆ What we learn from PK/PD information
 - ◆ What we learn from special populations
 - ◆ What we learn from interaction studies

- A proper confirmation study requires us to combine all of this information with what we learn from phase IIb to design the confirmatory study

- We need the White Space, “Thinking Time” (Bob Temple)

- At an individual study level
 - ◆ May not be faster – because speed is anathema to adaptive learning
 - ◆ May not be cheaper – we may need more doses to properly characterise dose response
 - EMAX models

- BUT
 - ◆ Reduce the risk of recycling
 - ◆ Shorten the whole development program
 - ◆ Deliver better information
 - ◆ Increase Phase III success

Learning has to do with Estimation

- Problems of controlling type I error (Gordon Lan)
- Problems with combining p-values from tests of different alternatives (Bob O'Neill)

Learning has to do with Estimation

- Multiple Comparison Methods Have No Place At All In The Interpretation of Data ? (A Quote from John Nelder)
- “the essential point to be stressed is that data analysis is concerned with exposing patterns not with making significance statements” (Nelder, 1971)
- “no scientific worker has a fixed level of significance at which, from year to year, and in all circumstances, he rejects hypotheses; he rather gives his mind to each particular case in the light of his evidence and his ideas” (Fisher, 1956)



THE FUTURE

The Benefits of the Adaptive Debate

■ Better planning

- ◆ Comparison of adaptive designs with “traditional designs” will improve the latter if they are the most appropriate”
- ◆ Sample Size Re-estimation
 - We don’t know enough about the nuisance parameters
 - Acknowledge that in planning
 - Uncertainty implies large sample sizes
 - Combine with early stopping for futility or efficacy

The Benefits of the Adaptive Debate

- Statisticians are not only at the table
 - ◆ There at the forefront
 - Declan Doogan “....impressed by how much statisticians can contribute ...”
 - ◆ Proactive, assertive

- Statisticians need to decide to which group they belong
 - ◆ “Some people make things happen”
 - ◆ “Some people watch things happen”
 - ◆ “Some people ask what has happened”

Profile of Adaptive Designs

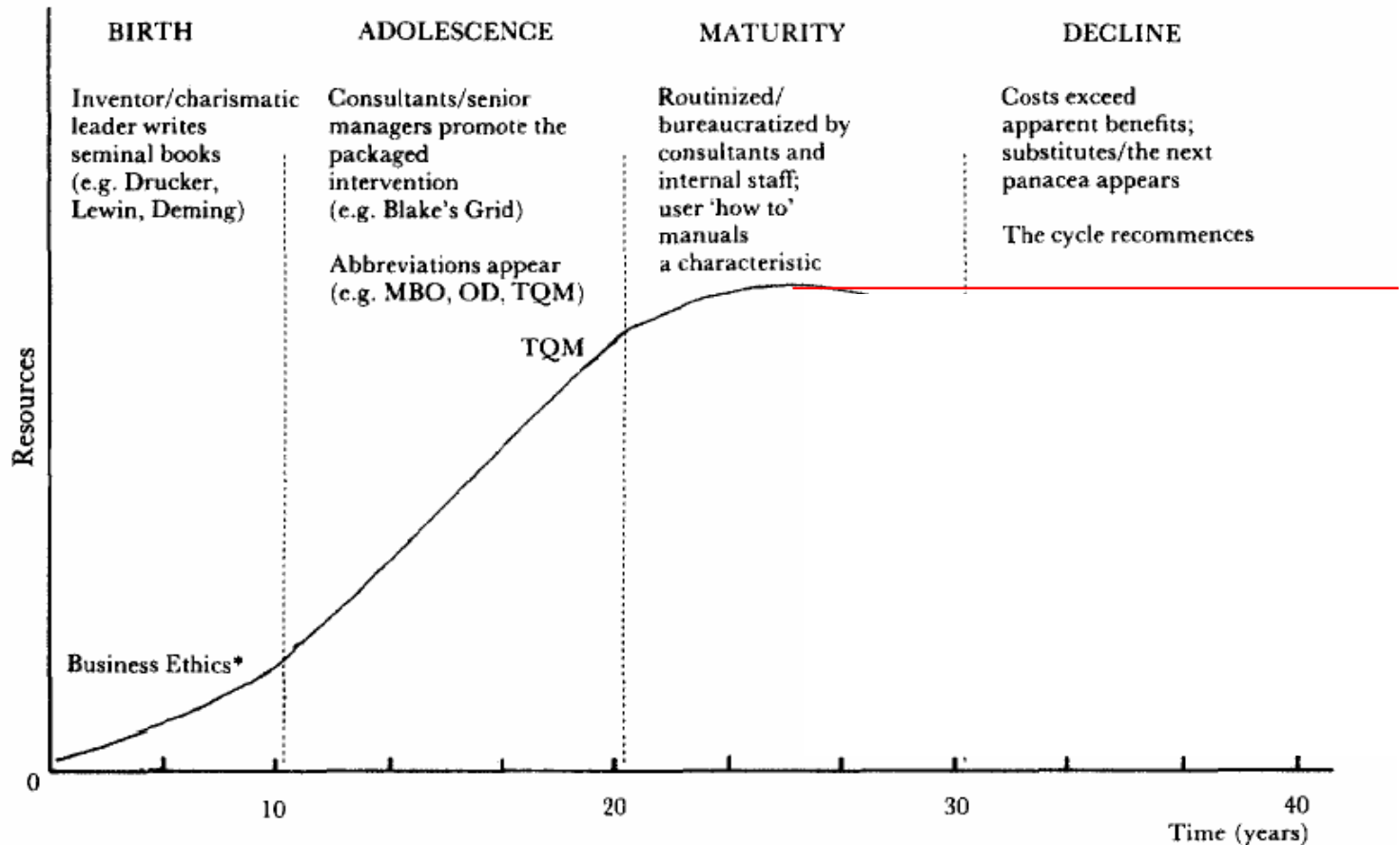


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