ESHO School on Clinical Hyperthermia,
Refresher, Vrängö
12th -13th September 2022

Clinical Trials in Hyperthermia: Their Interpretation and Impact on Integrating Hyperthermia into Clinical Practice

Prof. Niloy Ranjan Datta
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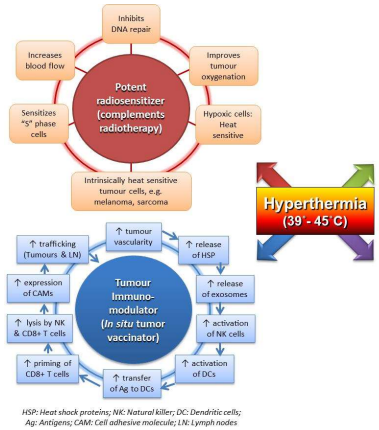
India

Developments in Hyperthermia

Thermoradiobiological Rationale



HSP: Heat shock proteins; NK: Natural killer; DC: Dendritic cells; Ag: Antigens; CAM: Cell adhesive molecule; LN: Lymph nodes

Interaction with Chemotherapeutic Agents

Independent: 5-Flurouracil, Methotrexate, Actinomycin D, Cytarabine, Taxanes,

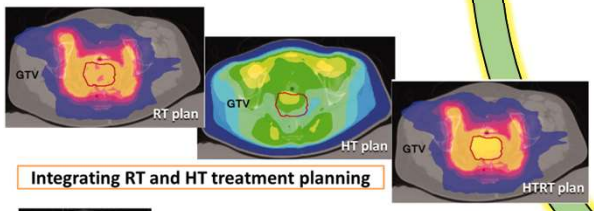
Additive: Doxorubicin, Cyclophosphomide, Ifosphomaide, Gemcitabine

Synergistic: Cisplatin, Carboplatin, Mitomycin C, Bleomycin

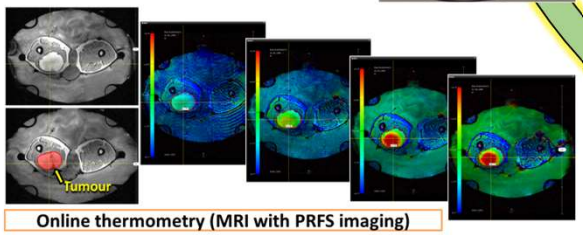
Nanoparticle based Hyperthermia

- Enhanced permeability & retention effect
- Closer proximity to tumour vasculature results in higher global parenchymal tumour temperature
- Heating " inside out" results in higher intratumoral temperature and reduced damage to normal tissue
- Sensitizes cancer stem cells
- Theranostics
- Could be designed to deliver targeted chemotherapeutic agents and radioactive tracers

HTRT planning & online thermometry



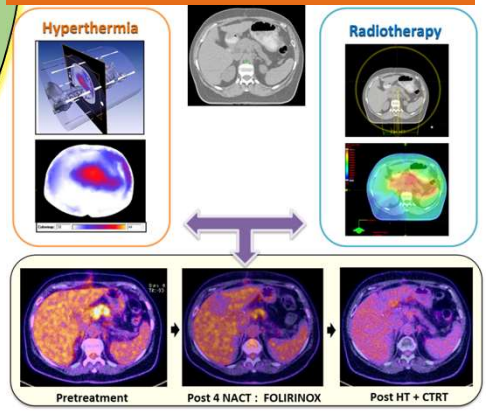
Integrating RT and HT treatment planning



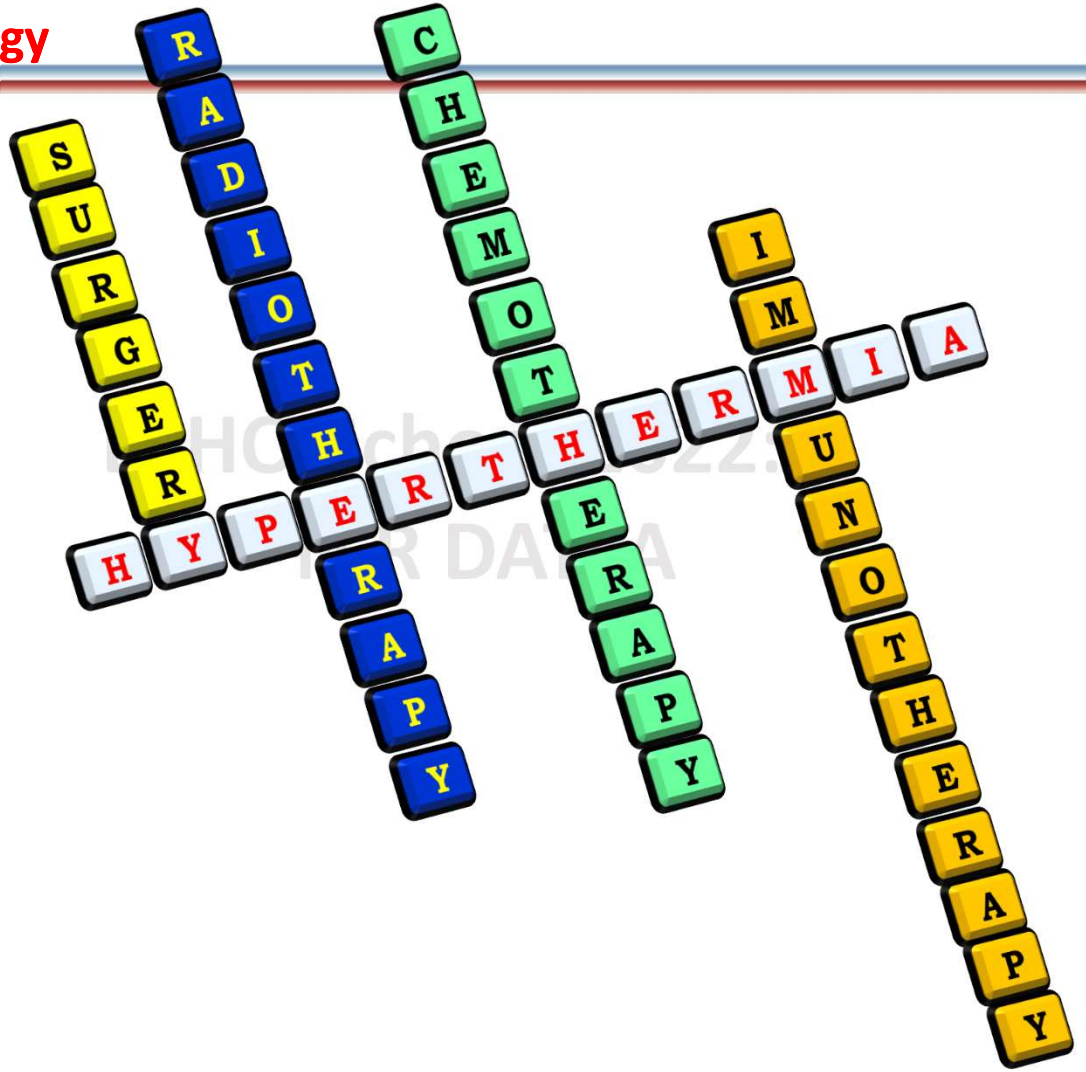
Online thermometry (MRI with PRFS imaging)

Superficial hyperthermia:

Deep hyperthermia



Integrating Hyperthermia
In Clinical Practice of Oncology

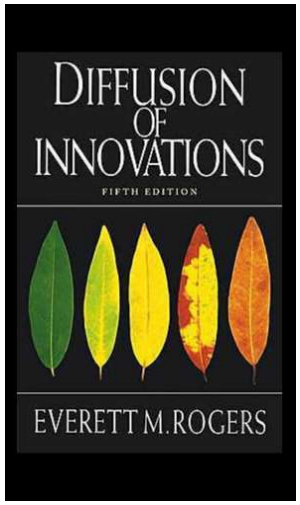


Hyperthermia today…

However ……

Hyperthermia is still NOT considered in the standard armamentarium for routine cancer therapy ?

"Law of Diffusion of Innovation"
As could be applied to "Acceptance of Hyperthermia"

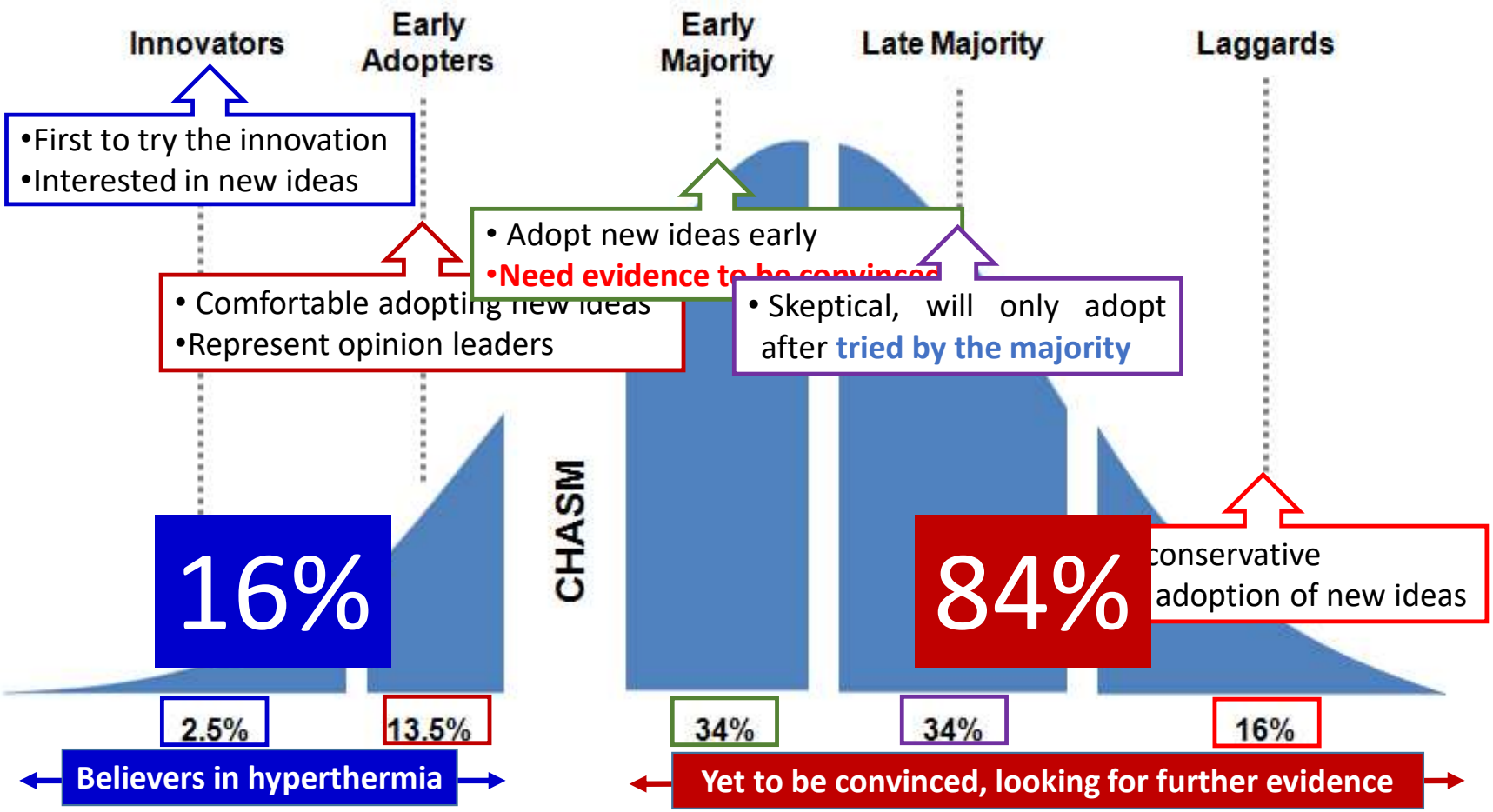


Law of "Diffusion of Innovation" - E.M. Rogers (1962)

Explains how over time an NEW idea gains momentum and diffuses (or spreads) to get widespread acceptance in specific population/ social system / health practices

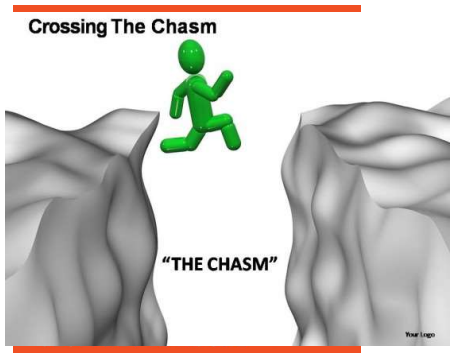
"Law of Diffusion of Innovation"

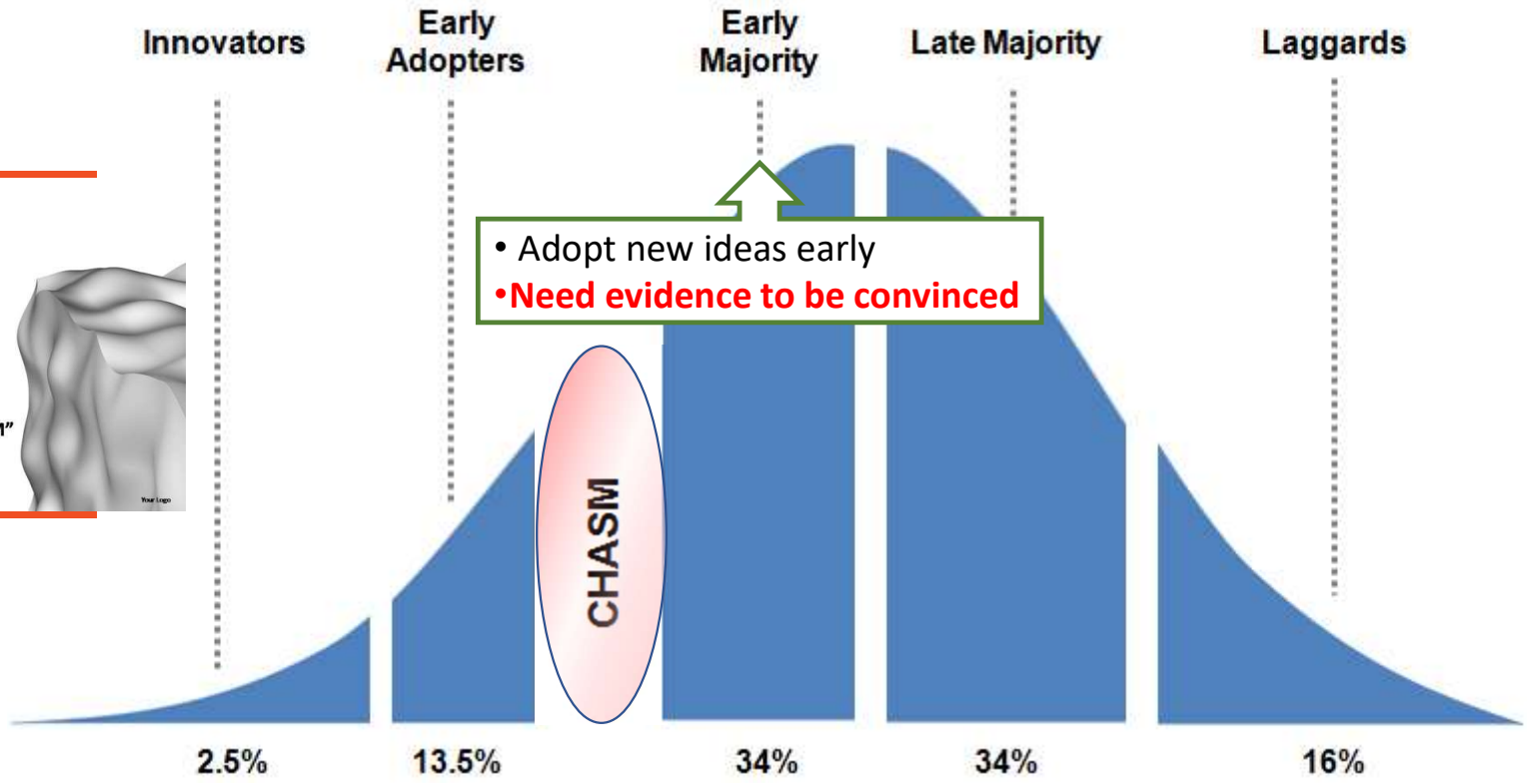
As could be applied to "Acceptance of Hyperthermia"



"Law of Diffusion Innovation"

As could be applied to "Acceptance of Hyperthermia"

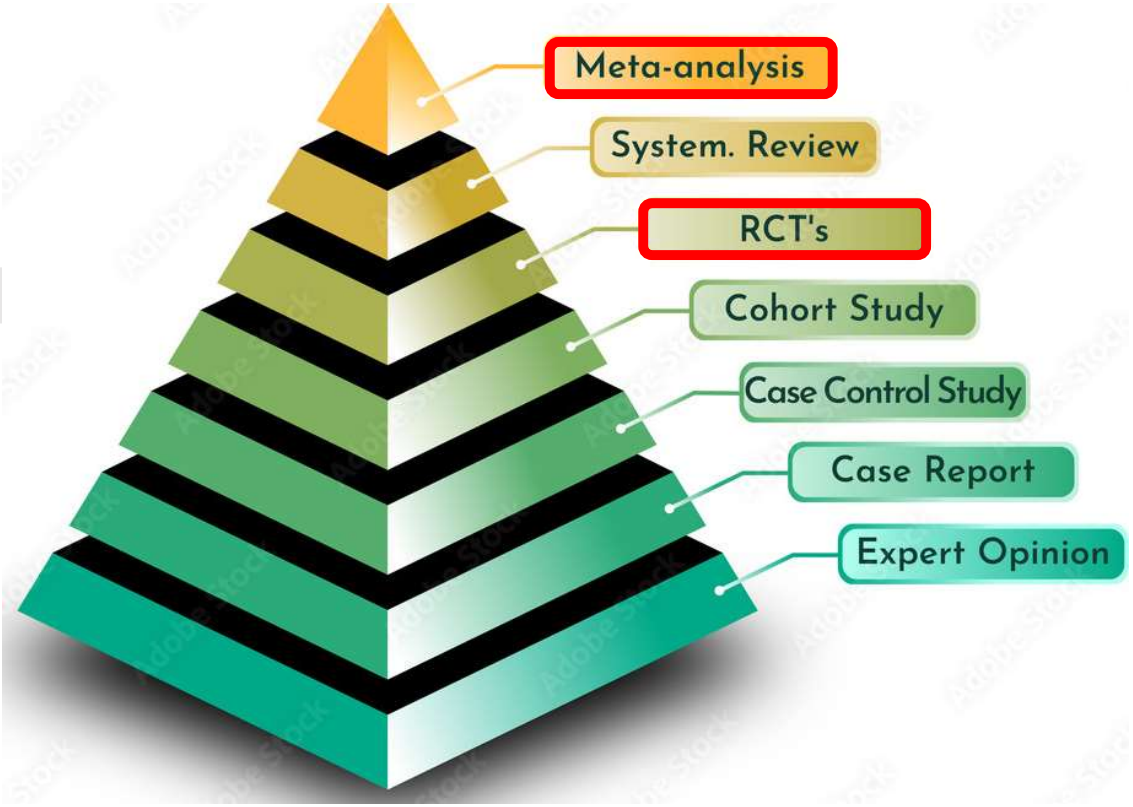




Need evidence to cross the "Chasm" and integrate hyperthermia into clinical oncology practice

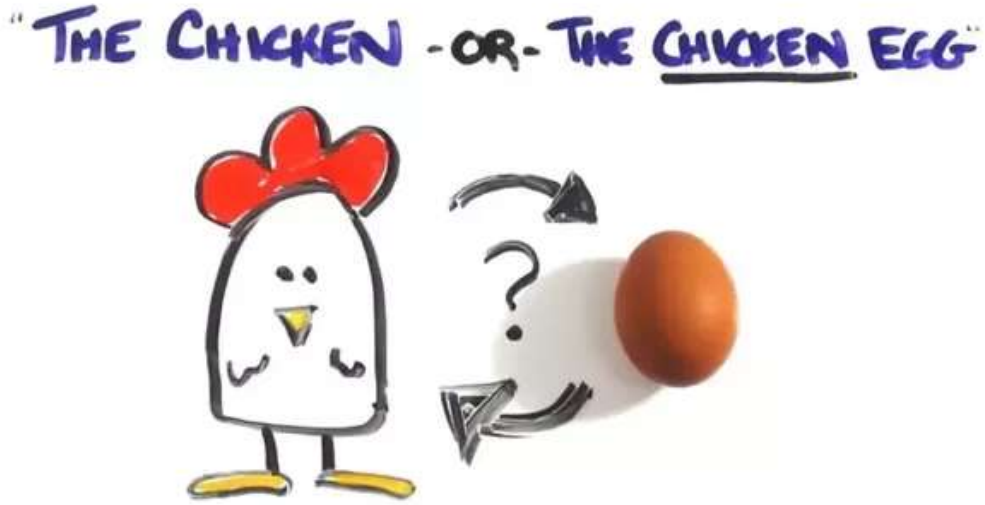
Clinical Practice of Medicine

Evidence Based Medicine



Randomized Clinical Trial – The Gold Standard and Basis of Evidence-Based Medicine

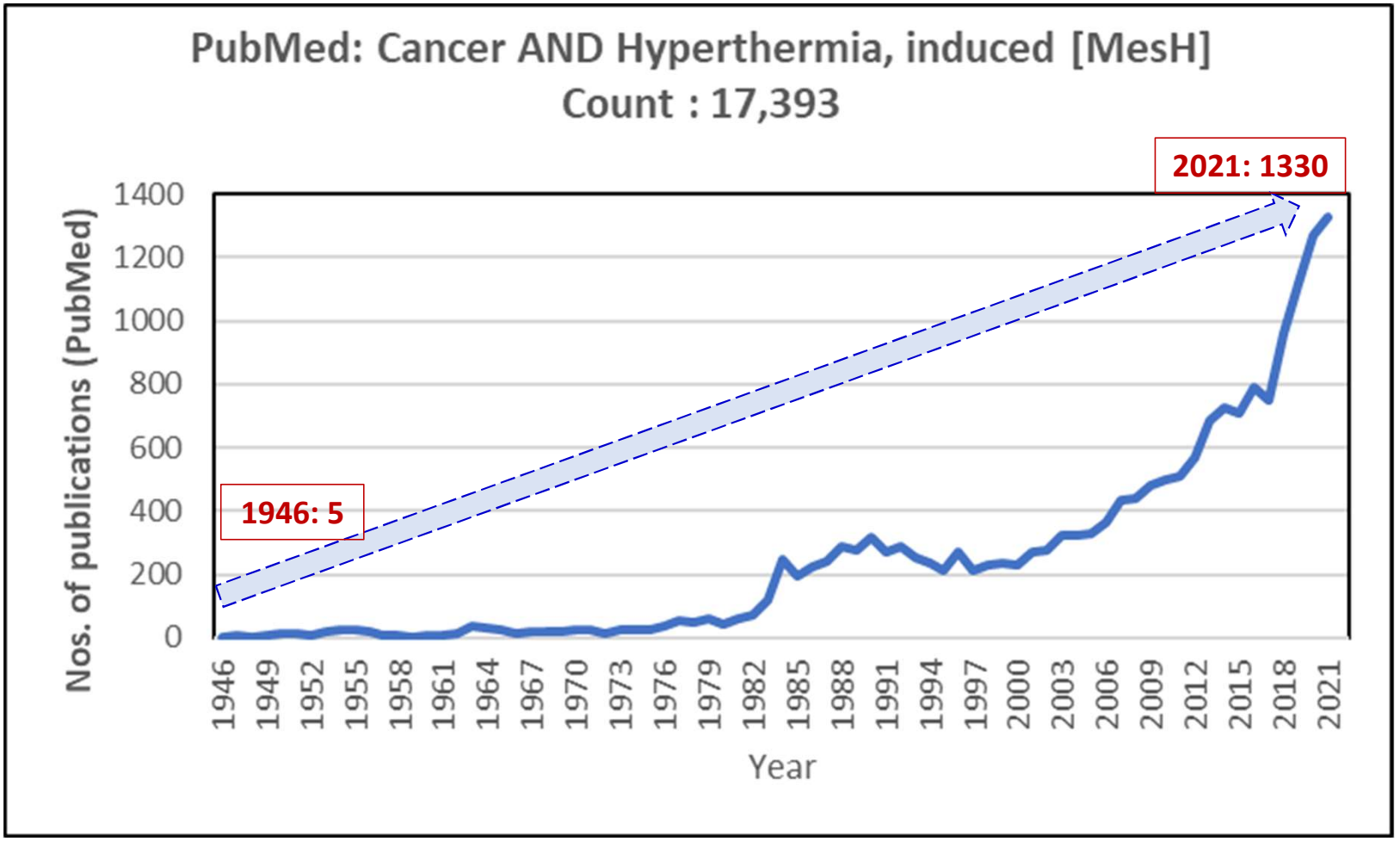
Clinical Practice of Medicine
Evidence Based Medicine



The Dilemma Towards Generating Evidence for Hyperthermia in Clinical Practice

Publications on Hyperthermia, Induced And Cancer

Hyperthermia … as on Sept 1, 2022



Randomized Clinical Trials

Hyperthermia … as on Sept 1, 2022

PubMed Search

(CANCER AND Hyperthermia, Induced **NOT HIPEC NOT HIVEC NOT HIFU, Filter Randomized Clinical Trial**)

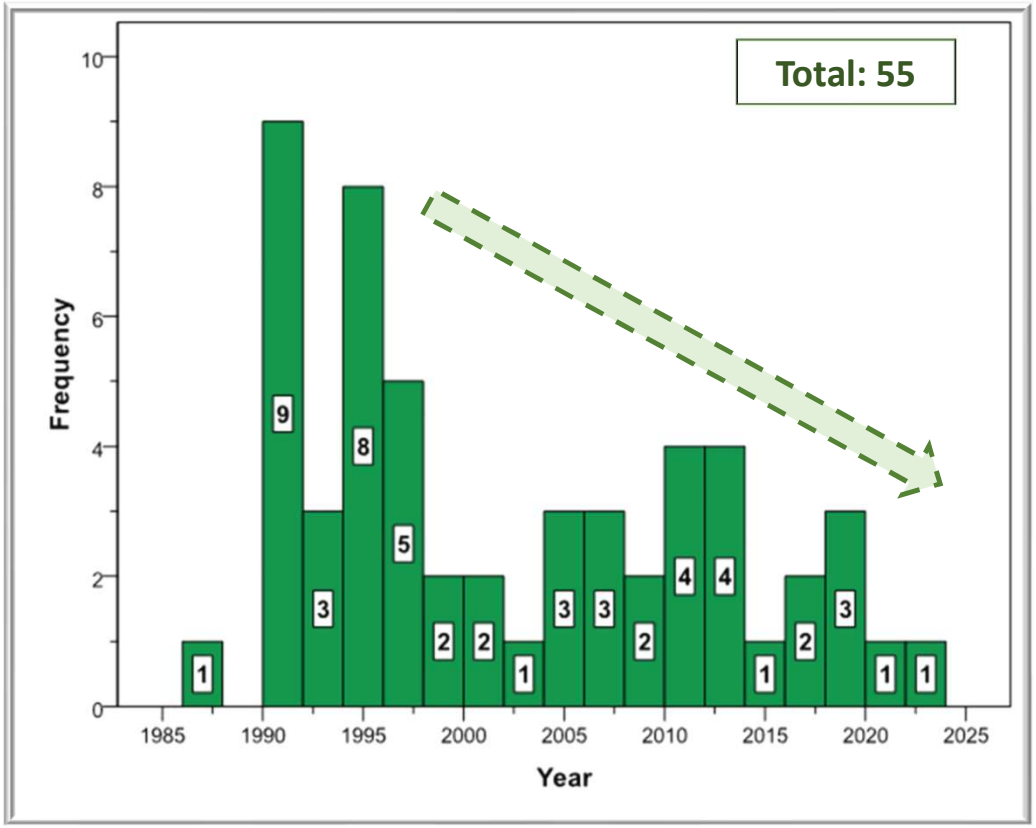
Randomized Controlled Clinical Trials with Hyperthermia

n = 55

(1987 – 2022)

Hand search Articles

(Only **Randomized Clinical Trials** with Hyperthermia)



Randomized Clinical Trials
Major Sites

Total randomized clinical trials : 55
Total number of patients : 6,615 (35-373)

Sites	Number of trials	Total patients
Locally advanced cancer cervix (LACC)	11	1406
Locally advanced head & neck cancers (LAHNC)	6	388
Cancer ano-rectum	6	578
Cancer breast (Recurrent)	5	542
Cancer nasopharynx	5	766
Cancer oesophagus	5	453

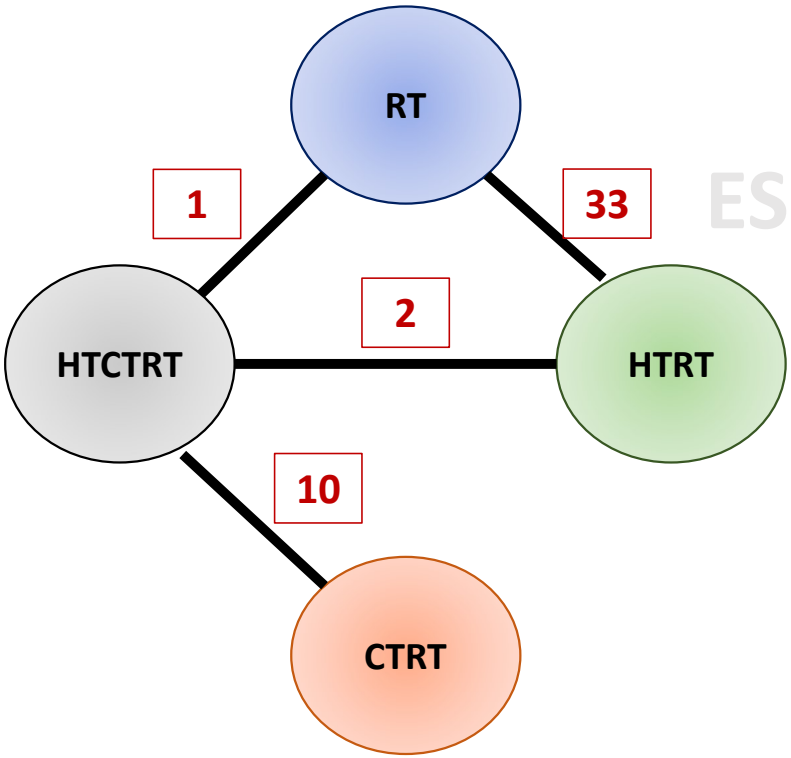
Nos. of trials	Sites
3	Lung, Uveal melanoma
2	Urinary bladder, Superficial cancers
1	Soft tissue sarcomas, Bone metastasis, pelvic tumours, glioblastoma multiforme, recurrent/ persistent tumours, melanoma, stomach

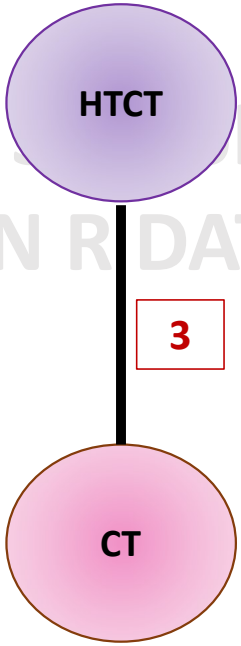
Randomized Clinical Trials

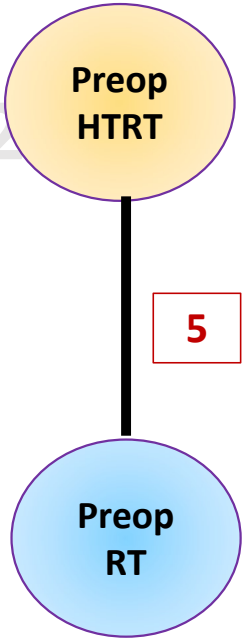
Treatment arms: Control and Study arms

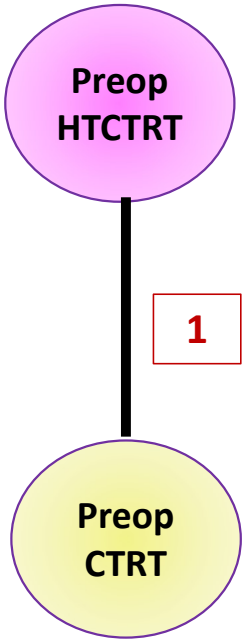
Hyperthermia (HT) and/or **Radiotherapy (RT)** and / or **Chemotherapy (CT)**

2 trials were 3-arm trial





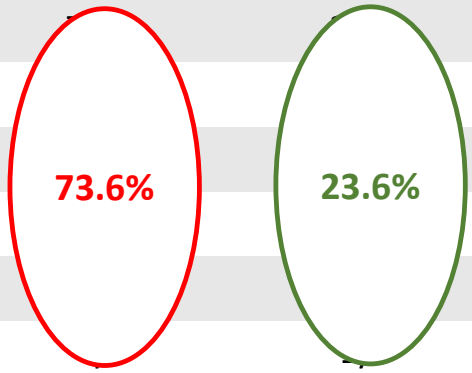




Randomized Clinical Trials

Treatment outcomes

Sites	Number of trials	Total patients	HT arm better	No difference	HT worse
Locally advanced cancer cervix (LACC)	11	1406			1/11
Locally advanced head & neck cancers	6	388			-
Cancer ano-rectum	6	578			-
Cancer breast (Recurrent)	5	542			-
Cancer nasopharynx	5	766			-
Cancer oesophagus	5	453			-



Locally advanced cancers of Head Neck, Breast and Cervix

Level I evidence with Hyperthermia

International Journal of Hyperthermia

http://informahealthcare.com/hth
ISSN: 0265-6736 (print), 1464-5157 (electronic)

Int. J. Hyperthermia, Early Online: 1–10
© 2015 Taylor & Francis. DOI: 10.3109/02656736.2015.1099746

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RESEARCH ARTICLE

Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis

Niloy R. Datta[1], Susanne Rogers[1], Silvia Gómez Ordóñez[1], Emsad Puric[1], & Stephan Bodis[1,2]

[1]Centre for Radiation Oncology, KSA-KSB, Kantonsspital, Aarau, Switzerland and [2]Department of Radiation Oncology, University Hospital, Zurich, Switzerland

(Datta NR et al., Int J Hyperthermia, 2016)

Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis

Niloy R. Datta, MD,* Emsad Puric, MD,* Dirk Klingbiel, PhD,† Silvia Gomez, MD,* and Stephan Bodis, MD*,‡

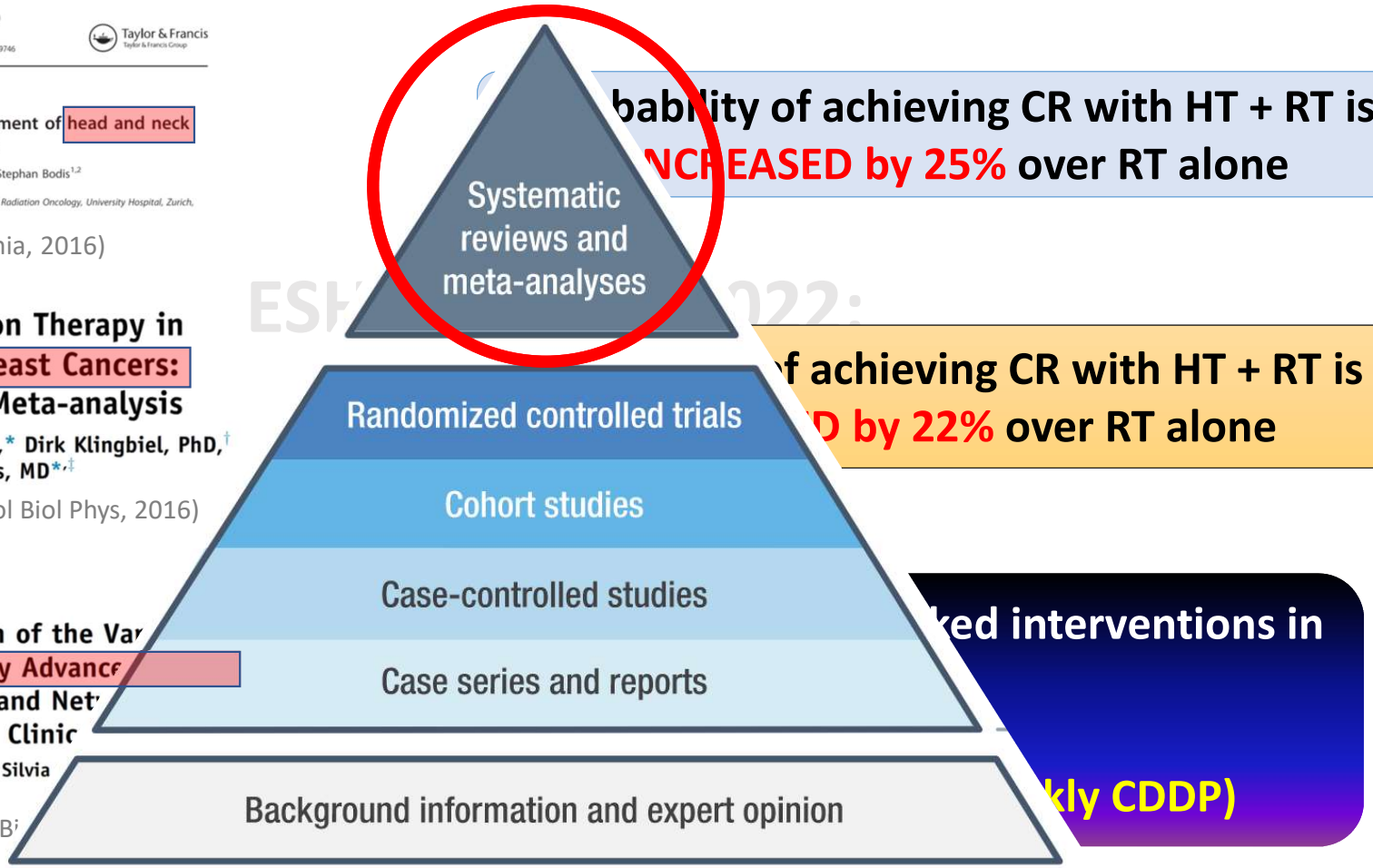
(Datta NR, et al., Int J Radiat Oncol Biol Phys, 2016)

Critical Review

Efficacy and Safety Evaluation of the Var... Therapeutic Options in Locally Advance... Cancer: A Systematic Review and Net... Meta-Analysis of Randomized Clinic...

Niloy R. Datta, MD,* Emanuel Stutz, MD,* Silvia ... and Stephan Bodis, MD*,†

(Datta NR et al, Int J Radiat Oncol Bi...



...bability of achieving CR with HT + RT is ...NCREASED by 25% over RT alone

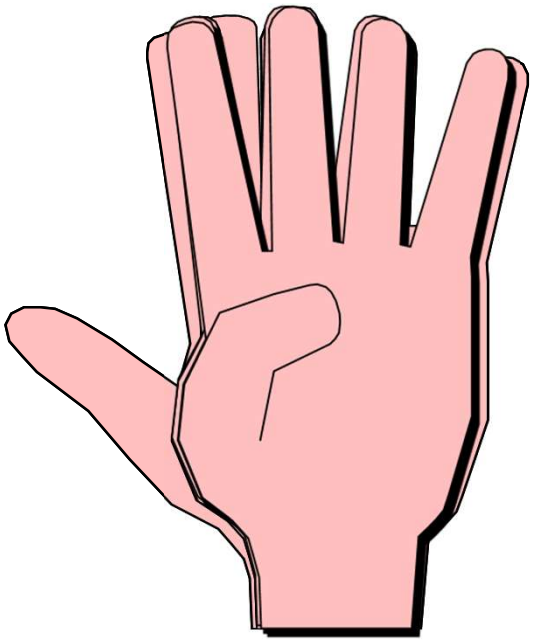
...f achieving CR with HT + RT is ...D by 22% over RT alone

...ked interventions in ...kly CDDP)

Well designed phase III randomized trials are the key building blocks for meta-analyses to generate Level I evidence

How to interpret the randomized trials ?

Key points for proposing new phase III randomized studies



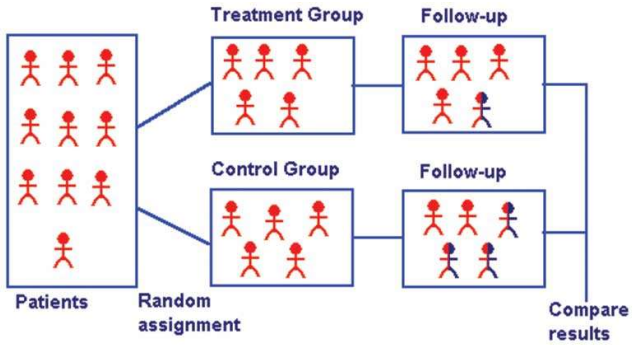
Design

Sample size calculation

Clinical Endpoints

Outcome analysis

Reporting



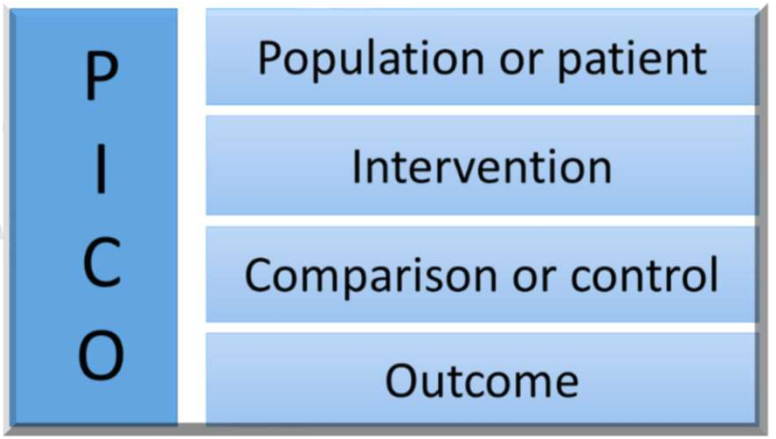
Clinical Trials

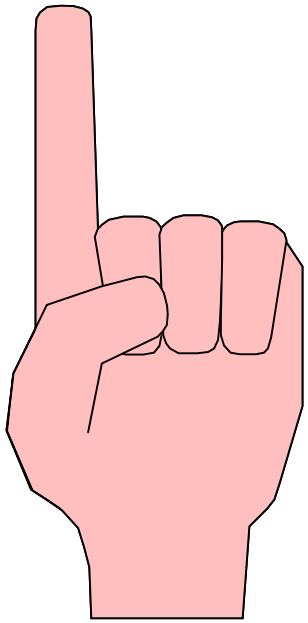
The key steps

Randomized Clinical Trials

Research question : The PICO

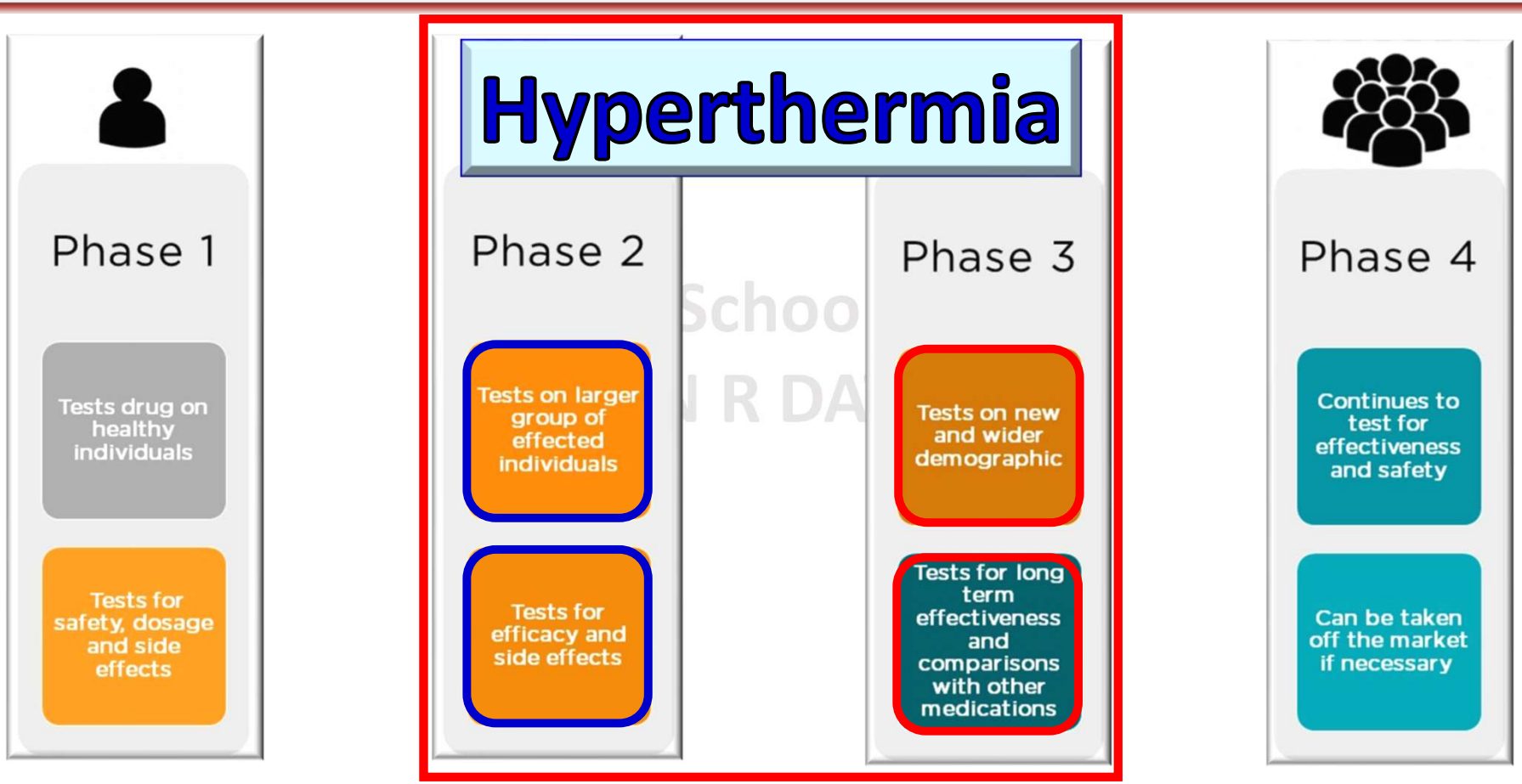
- **Primary research question to fill the gap in knowledge in the existing literature**
  - **P**atients: Specify a **well defined** population
  - **I**ntervention: HT + (RT ± CT ± S)
  - **C**omparison: Standard therapy (RT ± CT ± S)
  - **O**utcome: Define **specific and pragmatic** end points





Trial Design

Phases of Clinical Trials



Randomized Clinical Trials

Randomization …. An essential requirement

- **Uses allocation concealment** through randomizations
- **Eliminates** selection bias
- **Permits** use of probability theory – any difference in outcomes could be merely due to chance
- **Could blind identity** of intervention to the investigators, participants and evaluators
- **Method of randomization** should be clearly stated
  - Simple randomization
  - Block randomization
  - Stratified randomization

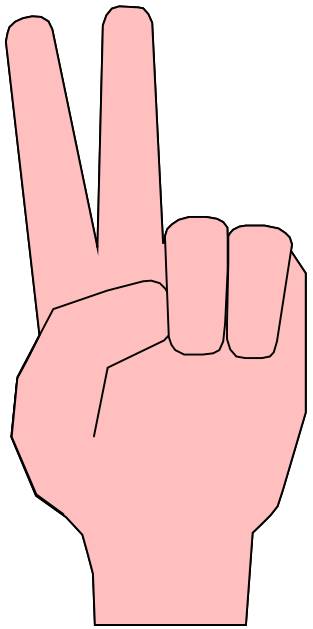
Randomized Clinical Trials

Blinding

- Blinding individual groups who can potentially introduce bias through knowledge of the treatment assignments
- Various types of blinded studies

Types of blinded trials	Patients	Clinicians	Data analysts
Unblinded / open label	×	×	×
Single blinded	Yes	×	×
Double blinded	Yes	Yes	×
Triple blinded	Yes	Yes	Yes

Single blinding not feasible for hyperthermia intervention



Sample Size Calculation

Randomized Clinical Trials

Sample size calculation

Based on

- Estimated outcomes in Study vs Control group
- Type 1 (α) error (False Positive error) (0.05)
- Type II (β) error (False Negative error) (0.1 - 0.2)
- Statistical power : 1 - β *(Ideally 80% or 90%)*

✓ Correct conclusion

Null Hypothesis / Conclusion	Real Difference	
	No	Yes
Null hypothesis (HO) **not rejected**	(1 – α) ✓	Type II (β)
Null hypothesis (HO) **rejected**	Type I (α)	✓ Power (1-β)

α = 0.05, indicates that, in 1/20 trials, we may **conclude a difference**, although in **real no difference exists**

β = 0.10, indicates that, in 1/10 trials, we may **conclude no difference**, although **a real difference exists**

Sample Size Calculation (SSC)

Parameters influencing SSC

Parameters required for SSC	Characteristics	Impact of parameters
Study design	Single arm / randomized	Larger samples for randomized studies
Test of hypothesis	Superiority, non-inferiority or equivalence	Larger samples for Non-inferiority or equivalence trials
Type I (α) or II (β) errors	Probabilities of false +ve/-ve	Larger the errors, larger the sample
Power	1 - β	Higher the power, larger is the sample
Effect size (difference)	Delta value (Expected difference between 2 arms)	Higher the delta, smaller is the required sample
Observed statistical significance	P value	Smaller the p value, larger the sample
Direction of statistical test	One-tailed/ two-tailed	Two-tailed have larger samples for same p value
Drop out rates	Add +10%	Add to SSC
Length of follow-up	For time-to-event variables	Longer the period, smaller is sample size

Randomized Clinical Trials

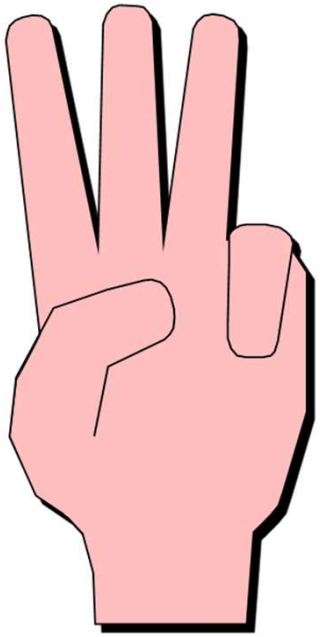
Sample size calculation

- Estimate the **% outcome** of **control group (P1)**
- Anticipate the **% outcome** of the **study group (P2)**
- Choose
  - **α** (typically **0.05**),
  - **β** values (typically **0.20**), Power 80%
- One / Two-tailed test
- Seek help from a statistician

Sample size in each group for comparing two proportions
(power=0.8, significance level=0.05)

	Percent for group 1									
% Group 2	0	10	20	30	40	50	60	70	80	90
10	74									
20	34	199								
30	21	62	293							
40	15	32	81	356						
50	11	20	39	93	387					
60	8	13	23	42	97	387				
70	6	10	14	23	42	93	356			
80	5	7	10	15	23	39	81	293		
90	4	5	7	10	14	20	32	62	199	
100	2	4	5	6	8	11	15	21	34	74

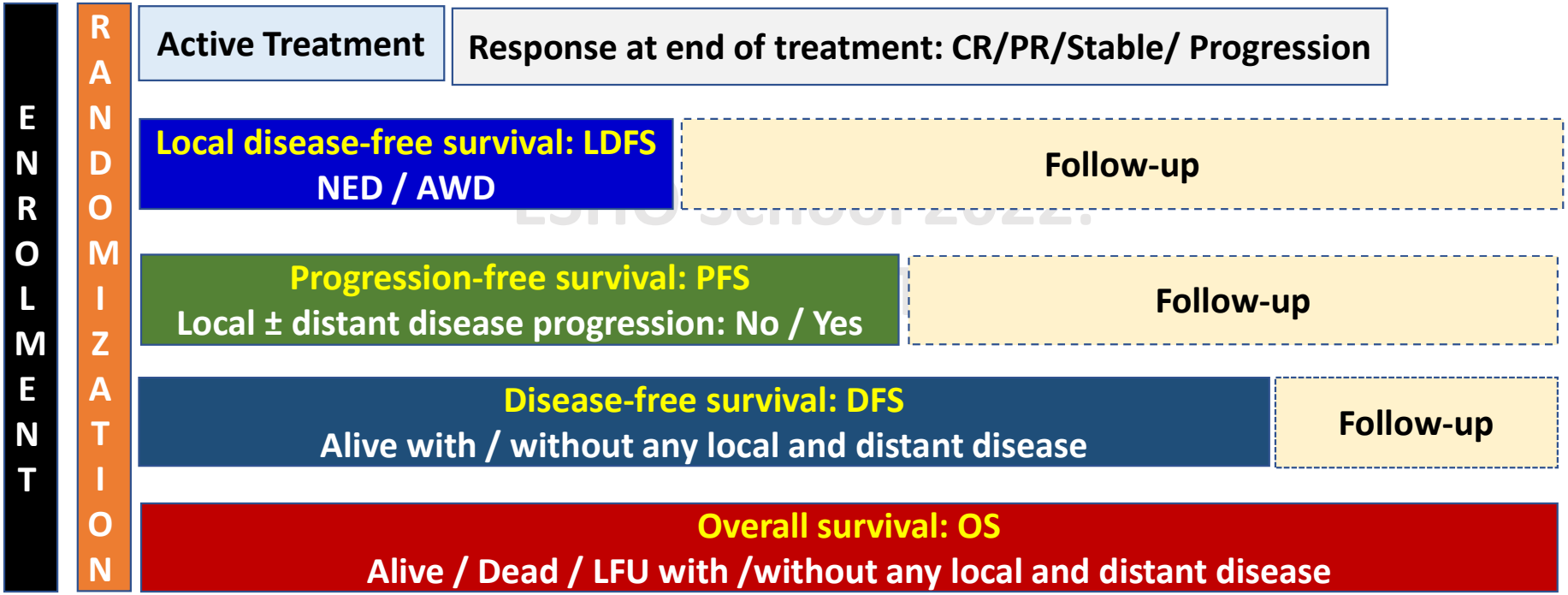
(http://www.3rsreduction.co.uk/html/6__power_and_sample_size.html)



Clinical End points

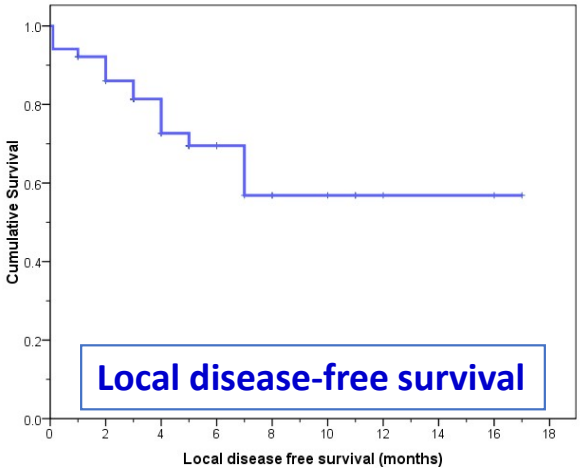
Randomized Clinical Trials

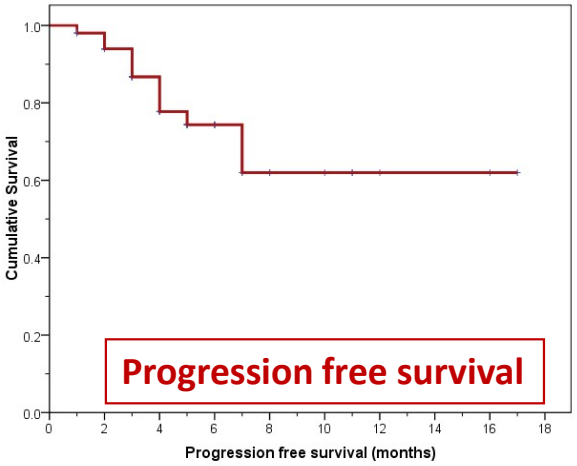
Endpoints of clinical significance

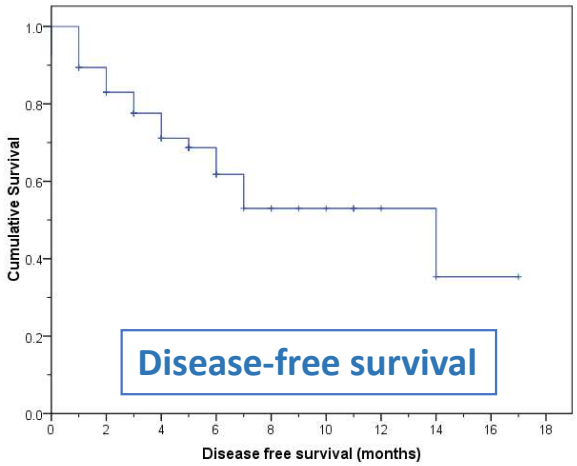


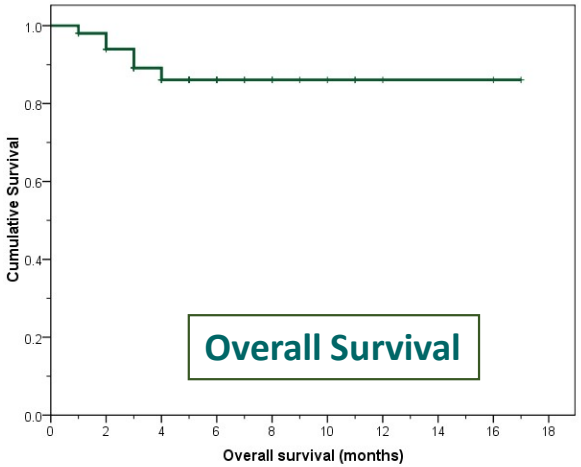
Survival end points

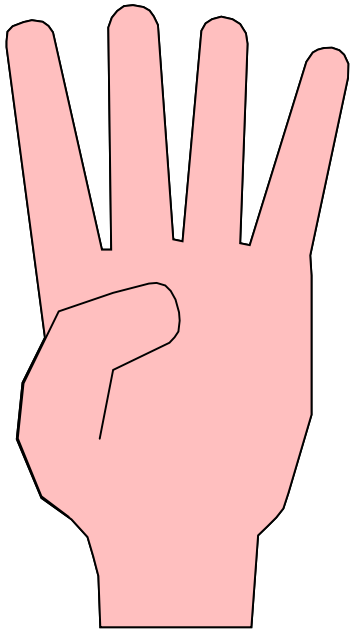
Kaplan-Meir plots











Outcome Analysis

Randomized Clinical Trials

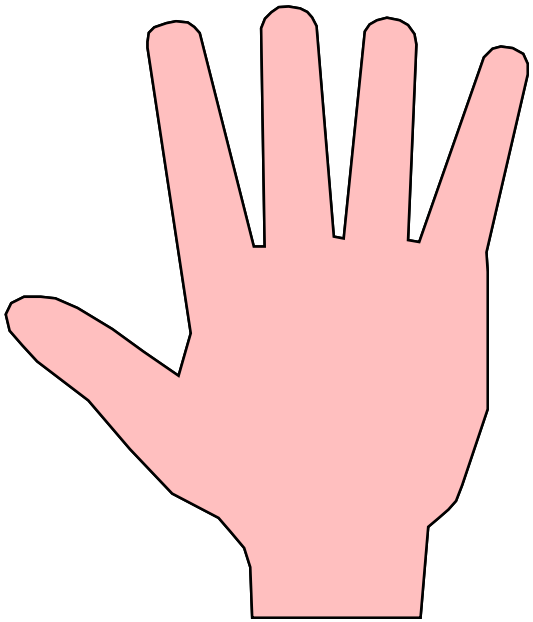
Intention-to-treat analysis

- Includes **all patients allocated and randomized** in both study and control groups
- **Preferred** analysis strategy
- **Problems:**
  - **Missing outcomes**
    - Carrying forward the last observation could **introduce bias**
    - Patients with missing outcomes : Should be **<10%** of randomized patients
  - **Nonadherence to protocol**
    - If excluded, may do "**Per protocol analysis**"

Randomized Clinical Trials

Per-protocol analysis

- Includes **only patients who have completed entire clinical trial/ have complete data**
- Patients **categorized according to actual treatment** received
- Weakness: **Reduced power** depending on non-compliance
- Could be **prone to bias**
- Could be carried out as a **secondary evaluation** to intention-to-treat analysis, results to be interpreted with caution



Reporting

Randomized Clinical Trials

Requirements : CONSORT Guidelines, 2010

CONSORT
TRANSPARENT REPORTING of TRIALS

Consolidated Standard of Reporting Trials

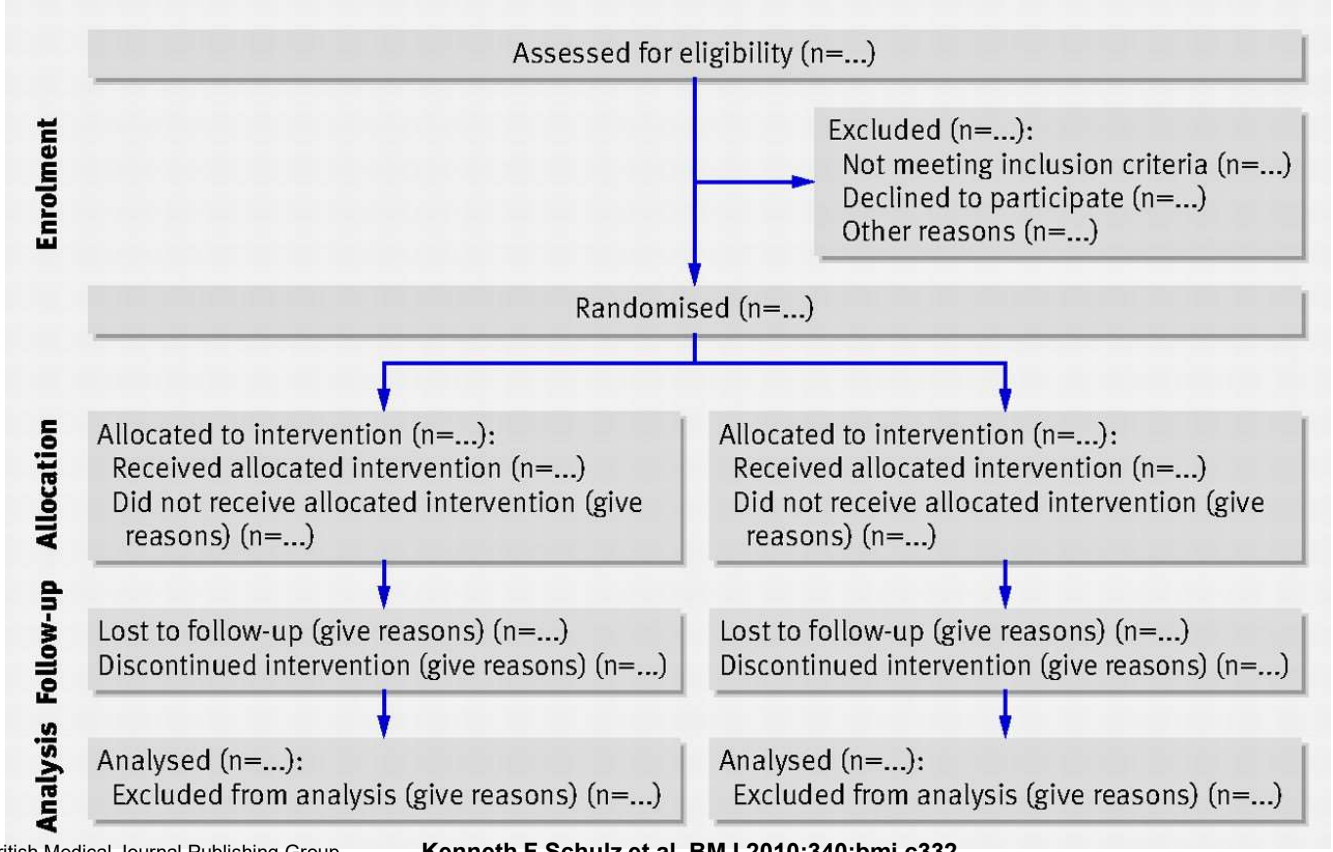
(www.consort-statement.org)

"Randomised controlled trials, when **appropriately designed, conducted, and reported**, represent the **gold standard in evaluating healthcare interventions**. However, randomised trials can yield biased results if they lack methodological rigour."……

Guidance for reporting all randomized trials

- Flow Chart of the Trial
- 25 item Checklist

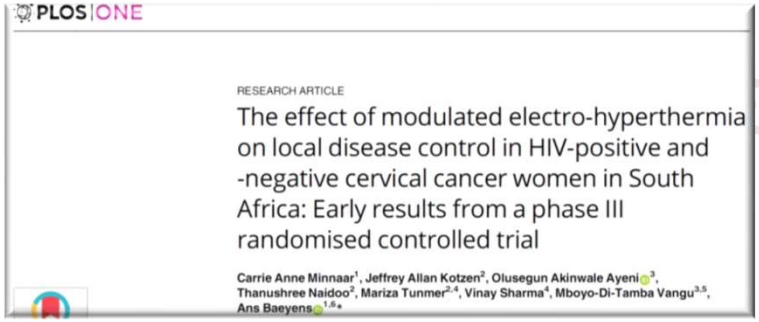
Flow diagram of the progress through the phases of a parallel randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis).



Kenneth F Schulz et al. BMJ 2010;340:bmj.c332

Randomized Clinical Trials… Participant flow Chart

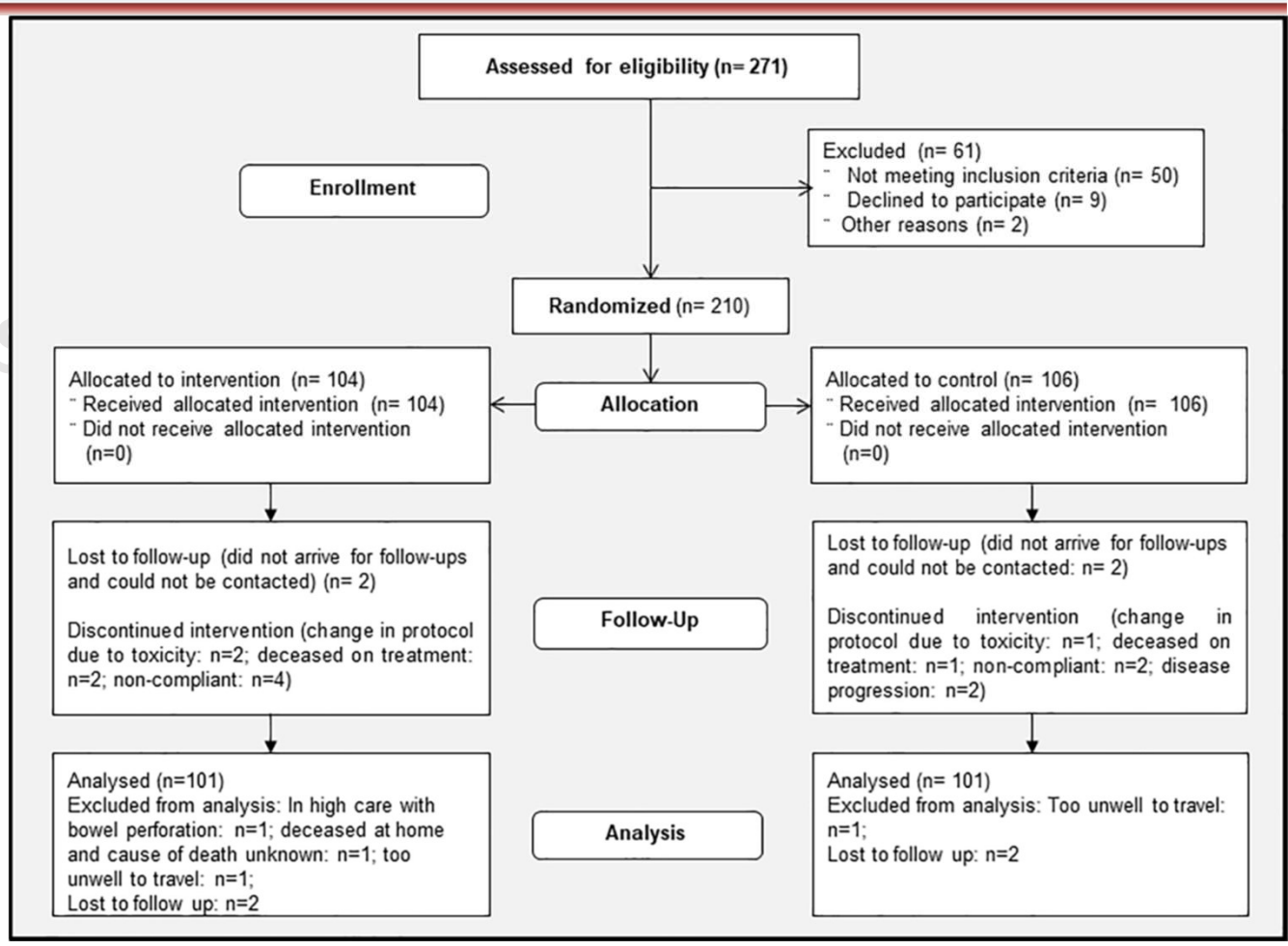
An example from Hyperthermia study (Phase III : CTHTRT vs CTRT)


PLOS ONE

RESEARCH ARTICLE

The effect of modulated electro-hyperthermia on local disease control in HIV-positive and -negative cervical cancer women in South Africa: Early results from a phase III randomised controlled trial

Carrie Anne Minnaar[1], Jeffrey Allan Kotzen[2], Olusegun Akinwale Ayeni[3], Thanushree Naidoo[2], Mariza Tunmer[2,4], Vinay Sharma[4], Mboyo-Di-Tamba Vangu[3,5], Ans Baeyens[1,6]*



Randomized Clinical Trials

Requirements : CONSORT Checklist, 2010…page 1

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

Randomized Clinical Trials

Requirements : CONSORT Checklist, 2010…page 2

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

So what's next ?

Radiotherapy &Oncology
European Society of Radiotherapy and Oncology

Editorial

The heat is (still) on – The past and future of hyperthermic radiation oncology

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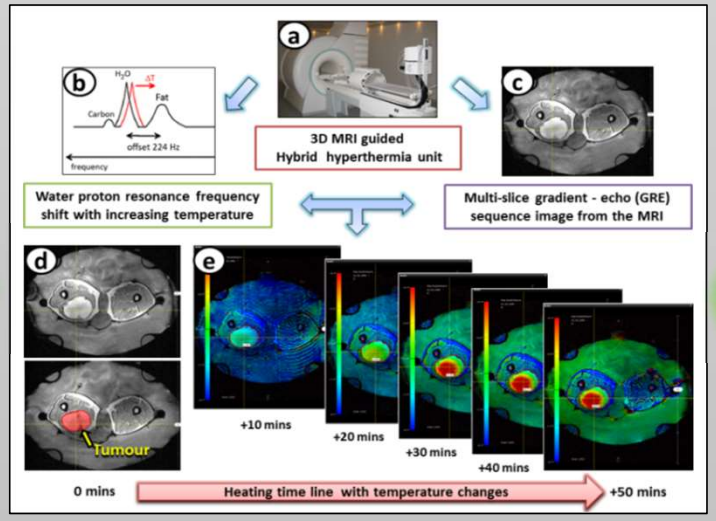
Nov 2013

Thus, the heat is still on – and we need to give full credit to the most powerful way of sensitizing ionizing radiation and thus once again focus on this not fully explored opportunity of combining radiotherapy with hyperthermia, but it must be done with an open mind and a cool head.

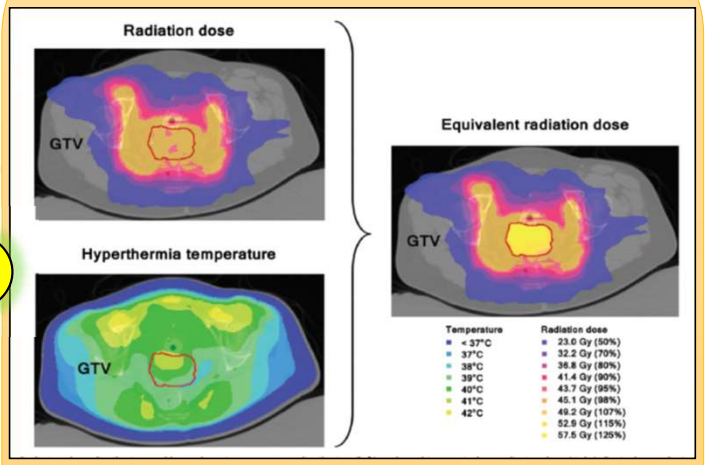
Hyperthermia

Hyperthermia treatment delivery and thermometry

HT Delivery



Non invasive thermometry



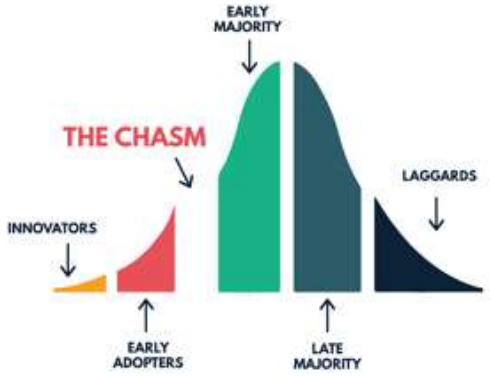
(van Leeuwen et al, Int J Hyperthermia, 2018)

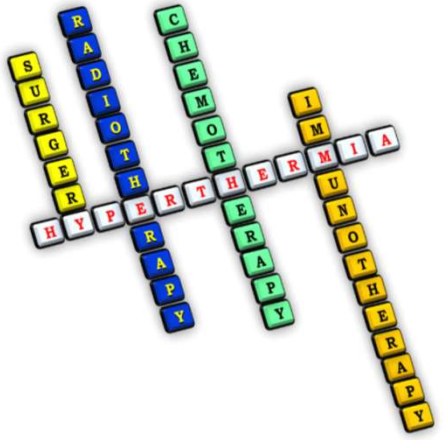
Treatment planning : HT + RT

(Gellermann J et al, Cancer 2006; Kok HP et al, Int J Hyperthermia 2016, Kok et al, Int J Radiat Oncol Biol Phy, 2017)

Take home message

- Practice of **Evidence Based Medicine** requires **phase III randomized** clinical trials to provide level I evidence with
  - Optimum **trial design**
  - Optimal **sample size** with $\alpha = 0.05$, $\beta = 0.20$
  - Optimal and **rationale endpoints**
  - Perform **"Intent-to-analysis"** for all endpoints
  - Trial reporting as per **CONSORT guidelines**
- Well designed, phase III randomized trials would help to **"Cross the Chasm" and facilitate** integrating hyperthermia in clinical oncology practice





(niloydatta@mgims.ac.in)