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EPICENE / Epidemiology of cancer and environmental exposures

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CENTRE RÉGIONAL DE LUTTE CONTRE LE CANCER DE BORDEAUX ET DU SUD-OUEST

UNICANCER
MEMBRE DU GROUPE

The DATECAN initiative

Definition and Assessment of Time-to-event Endpoints in CANcer trials

Carine BELLERA
INSERM U1219 et Institut Bergonié, Bordeaux
On behalf of the DATECAN steering committee

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Genesis (1)

- Design of randomized cancer trials → Classical questions
  - Which endpoint to assess treatment efficacy
    - OS
    - PFS, TTP, Time to metastasis, time to treatment failure, etc
  - Standardized definition for the primary endpoint?
  - Data for the primary endpoint in the control arm?

Genesis (2)

- Survival endpoints in published cancer randomized trials *(Mathoulin et al. J Clin Oncol 2008)*
  - Mutliple endpoints throughout the literature
  - Endpoints often poorly defined

184 defined survival endpoints among 104 phase III trials	N	%
Overall survival	101	55
Progression-free survival	27	15
Disease-free survival	18	10
Time to progression	16	9
Relapse-free survival	10	5
Event-free survival	12	6

	Articles (n = 125)	
Key Point	No.	%
Starting point	98	78
Event of interest	99	79
Censor	73	58
All 3 key points	65	52

Genesis (3)

COMMENTARY

Design and Endpoints of Clinical Trials in Hepatocellular Carcinoma

Josep M. Llovet, Adrian M. Di Bisceglie, Jordi Bruix, Barnett S. Kramer, Riccardo Lencioni, Andrew X. Zhu, Morris Sherman, Myron Schwartz, Michael Lotze, Jayant Talwalkar, Gregory J. Gores; for the Panel of Experts in HCC-Design Clinical Trials

COMMENTARY

J Natl Canc

Endpoints in Adjuvant Treatment Trials: A Systematic Review of the Literature in Colon Cancer and Proposed Definitions for Future Trials

Cornelis J. A. Punt, Marc Buyse, Claus-Henning Köhne, Peter Hohenberger, Roberto Labianca, Hans J. Schmoll, Lars Påhlman, Alberto Sobrero, Jean-Yves Douillard

J Natl Cancer Inst 2007;99:998–1003

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Proposal for Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials: The STEEP System

Clifford A. Hudis, William E. Barlow, Joseph P. Costantino, Robert J. Gray, Kathleen I. Pritchard, Judith-Anne W. Chapman, Joseph A. Sparano, Sally Hunsberger, Rebecca A. Enos, Richard D. Gelber, and Jo Anne Zujewski

Genesis (4)

- Published definitions of survival endpoints
  - Without consensus
  - Not often used
  - Few cancer sites

- Consequences: difficulty for the interpretation
  - Comparison between trials
  - Different conclusions according to different definitions

- Example: PETACC 03 *(Van Cutsem E et al. J Clin Oncol 2009)*
  - irinotecan / 5-fluorouracil (5-FU) / folinic acid (FA) versus 5-FU/FA in stage III colon cancer
  - DFS (with second primary tumors) → Significant difference
  - DFS (without second primary tumors) → No significant difference

Genesis (5)

- 2008-2009: launch of the DATECAN inititative
- Statisticians from French Comprehensive Cancer Centers (CLCC) + European Organization for Research and Treatment of Cancer (EORTC)
- **Goal: improvement of the statistical methods & design in randomized cancer trials with a focus on:**
  - **The standardization of the definition of time-to-event endpoints – DATECAN-1**
  - Surrogacy assessment – DATECAN-2
  - Specific populations – Elderly – DATECAN-Elderly

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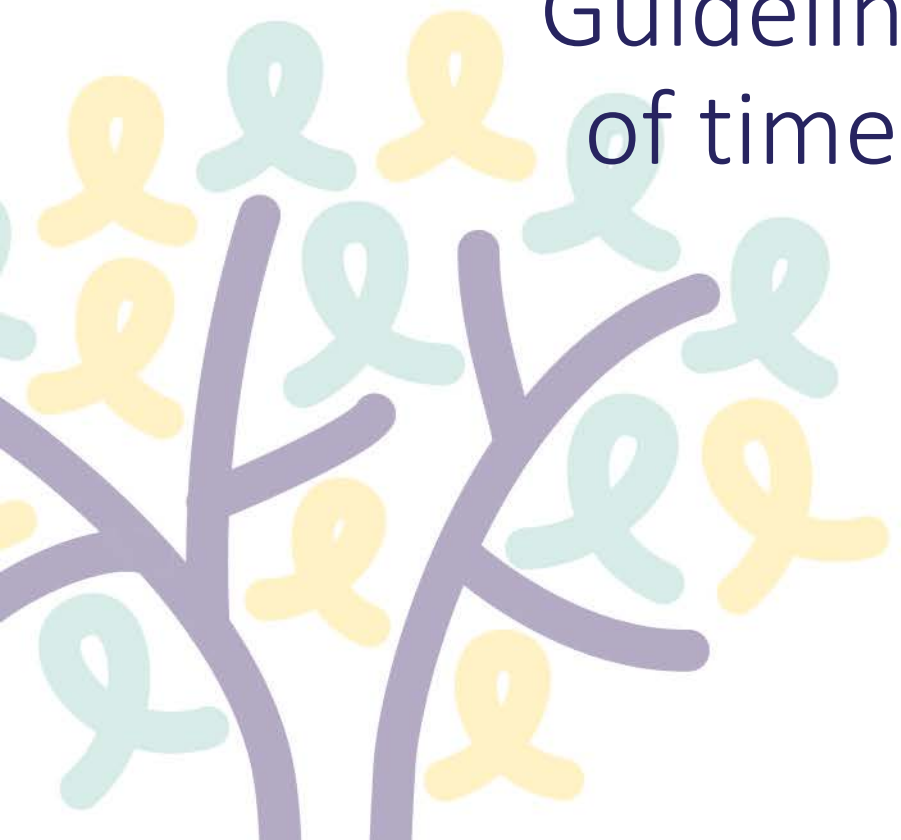
Guidelines for the definition of time-to-event endpoints

DATECAN-1 project



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DATECAN-1: Guidelines for survival endpoints

- **D**efinition and **A**ssessment of **T**ime-to-event **E**ndpoint in **CAN**cer trials
  → Definition of events to be accounted for in the definition of time-to-event endpoints

- Methods *(Bellera et al. Eur J Cancer 2013)*
  1. Identification of selected cancer sites for which guidelines are needed
     - Less interest: Adv. Prostate cancer, lymphoma
     - Primary interest: sarcoma/GIST, pancreas, breast, renal cell K, and other.
  2. For each cancer site, development of guidelines :
     - Identification of relevant endpoints to be defined → lit. rev.
     - Consensus process with iterative feedback
       - expert opinion obtained in a systematic manner
       - 2 rounds of questionnaires + 1 physical meeting
     - International and multidisciplinary panels of experts (oncologist, surgeon, radiotherapist, biostatistician, epidemiologists …)

Table 1. Time-to-event end points considered for the elaboration of guidelines for their definitions, and clinical events to be considered for inclusion in definitions

Time-to-event end points
Disease-specific survival (DSS)
Disease-free survival (DFS)
Relapse-free survival (RFS)
Locoregional relapse-free survival (LRRFS)
(Distant) metastasis-free survival (DMFS)
Failure-free survival (FFS)
Progression-free survival (PFS)
Local progression-free survival (LPFS)
Metastatic progression-free survival (MPFS)
Time-to-treatment failure (TTF)
Time to progression (TTP)
Time-to-local progression (TTLP)
Time-to-locoregional progression (TTLRP)
Time-to-distant progression (TTDP)
Clinical events
Death
Death related to primary cancer/to progression
Death related to a second cancer
Death related to protocol treatment
Death related to other causes
Unknown cause of death
End of treatment
Due to toxicity related to treatment
Due to toxicity unrelated to treatment
Loss of follow-up
Relapse/recurrence/progression
Local
Regional
Metastatic
Second sarcoma cancer (or second GIST)
Second nonsarcoma cancer (or second non-GIST)

Bellera et al. Annals Oncol 2014

DATECAN-1: Guidelines for survival endpoints

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DATECAN-1: questionnaire – 1st round

Please indicate on a scale of ***1 (totally disagree)*** to ***9 (totally agree)*** whether the following clinical events (first column) should be regarded as events in the definition of ***failure-free survival***. Please place one a **tick** ✓ **in each row.**

	Totally disagree								***Totally agree***
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Death related to primitive cancer / to progression									
Death related to a second cancer									
Death related to protocol treatment									
Death related to other causes									
Death related to unknown cause									
End of treatment due to tox. related to treatment									
End of treatment due to tox. unrelated to treatment									
Lost to follow-up									
Local relapse / recurrence									
Local progression									
Regional Relapse / recurrence									
Regional progression									
Appearance of metastases									
Progression of metastases									
Second sarcoma cancer									
Second non sarcoma cancer									

DATECAN-1: questionnaire – 2nd round

Please indicate on a scale of ***1 (totally disagree)*** to ***9 (totally agree)*** whether the following clinical events (first column) should be regarded as events in the definition of ***time to local progression***. Please place one a **tick** ✓ **in each row.**

	1st round			*2nd Round*								
	All experts		*Your answer*	*Totally disagree*								*Totally agree*
	Median	Min - Max		1	2	3	4	5	6	7	8	9
Death related to primitive cancer / to progression	5	1 - 9										
Death related to a second cancer	1	1 - 9										
Death related to protocol treatment	1	1 - 9										
Death related to other causes	1	1 - 9										
Death related to unknown cause	1	1 - 9										
End of treatment due to tox. related to treatment	1	1 - 6										
End of treatment due to tox. unrelated to treatment	1	1 - 4										
Lost to follow-up	1.5	1 - 9										
Local relapse / recurrence	9	2 - 9										
Local progression	9	9 - 9		*Consensus reached: consider as an event - Scoring not needed*								
Regional Relapse / recurrence	9	1 - 9										
Regional progression	1	1 - 9										
Appearance of metastases	1	1 - 3		*Consensus reached: do not consider as an event. Scoring not needed*								
Progression of metastases	1	1 - 6										
Second sarcoma cancer	1	1 - 9										
Second non sarcoma cancer	1	1 - 9										

DATECAN-1: Scoring process (HAS recommendations)

Opinion on the event		Median score	Distribution of scores
Appropriate to include the event	Strong consensus	≥ 7	All responses between 7-9, apart from up to two missing or outliers <7.
	Relative consensus	≥ 7	All responses between 5-9, apart from up to 2, missing or <5 (2 missing or two response <5 or one missing and one <5)
Inappropriate to include the event	Strong consensus	≤ 3	All responses between 1-3, apart from up to two missing or outliers >3.
	Relative consensus	≤ 3.5	All responses between 1-5, apart from up to two missing or outliers >5.
Uncertain	**Indecision**	4 – 6.5	Irrespective of responses.
	No consensus	≥ 7	At least three scores <5 or missing
		≤ 3.5	At least three scores >5 or missing

DATECAN-1: Guidelines for survival endpoints

- **D**efinition and **A**ssessment of **T**ime-to-event **E**ndpoint in **CAN**cer trials
  → Definition of events to be accounted for in the definition of time-to-event endpoints

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	No detectable disease					Detectable disease				All settings				
	DFS	RFS	LRFS	TLR	DMFS	PFS	TTP	TLP	MPFS	CSS	TTF	FFS	TPSD	TQL
Local relapse/recurrence	X	X	X	X	E						X	X	E	E
Local progression						X	X	X	E		X	X	E	E
Regional relapse/recurrence	X	X	X	X	E						X	X	E	E
Regional progression						X	X	X	E		X	X	E	E
Progression of metastases/distant progression						X	X	E	X		X	X	E	E
Appearance/occurrence of distant metastases	X	X	E	E	X						X	X	E	E
Appearance/occurrence of liver metastases	X	X	E	E	X	X	X	E	X		X	X	E	E
Appearance/occurrence of non-liver metastases	X	X	E	E	X	X	X	E	X		X	X	E	E
Second pancreatic cancer	X	E	E	E	E	X	E	E	E		X	X	E	E
Second non-pancreatic cancer	E	E	E	E	E	E	E	E	E		E	E	E	E
Death related to primary cancer	X	X	X	E	X	X	X	X	X	X	X	X	X	X
Death related to a second cancer	X	X	X	E	X	X	E	E	X	X	E	X	X	X
Death related to protocol treatment	X	X	X	E	X	X	E	E	X	X	E	X	X	X
Other cause of death	X	X	X	E	X	X	E	E	X	E	E	X	X	X
Unknown cause of death	X	X	X	E	X	X	E	E	X	X	E	X	X	X
End of treatment due to…	E	E	E	E	E	E	E	E	E		X	NC	E	E
Occurrence of WHO PS Grade 3-4-5	E	E	E	E	E	E	E	E	E		E	E	X	X
QoL score deterioration*													E	X
Lost to follow-up	E	E	E	E	E	E	E	E	E	E	E	E	E	E

Pancreatic cancer

Bonnetain et al. Eur . J. Cancer 2014

Table 2. DATECAN guidelines for standardized definitions of time-to-event end points in randomized controlled trials assessing treatment of sarcomas and GIST

Time-to-event end points	Clinical events to be included in definition of the time-to-event end points								
	Death due to primary cancer (primary site)	Death due to primary cancer (meta. disease)	Death due to second cancer	Death due to protocol treatment	Death due to other causes	Death due to unknown cause	Local events	Regional events	Metastatic events
All settings									
Disease-specific survival	X	X		X					
Locoregional relapse-free survival	X	X	X	X	X	X	X	X	
Time to progression	X	X					X	X	X
Time-to-local progression	X						X		
Time-to-locoregional progression	X						X	X	
Time-to-distant progression		X							X
Time-to-treatment failure	X	X		X			X	X	X
Adjuvant setting									
Disease-free survival	X	X	X	X	X	X	X	X	X
(Distant) metastasis-free survival	X	X	X	X	X	X			X
Metastatic setting									
Progression-free survival	X	X	X	X	X	X	X	X	X
Local progression-free survival	X	X	X	X	X	X	X		
Metastatic progression-free survival	X	X	X	X	X	X			X

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Sarcoma & GIST

Bellera et al. Annals Oncol. 2014

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Table 2. DATECAN guidelines for clinical events to be included in the definitions of time-to-event end points in randomized clinical trials assessing treatments for breast cancer

Setting	Recommended Time-to-event end point	Causes of death included in definition					Clinical events included in definitions							
		From breast cancer	From non-breast cancer cause	Related to protocol treatment	From any cause	From unknown cause	Invasive ipsilateral breast tumor recurrence/ progression	Local invasive recurrence/ progression	Regional invasive recurrence/ progression (M+: regional progression)	Invasive contra lateral breast cancer	Appearance/ occurrence of metastases/ distant recurrence	Second primary invasive cancer (non-breast cancer)	Ipsilateral DCIS	Contra lateral DCIS
Non- metastatic	BCSS	X		NC										
	iDFS	X	X	X	X	X	X	X	X	X	X	X	X	X
	D-DFS	X	X	X	X	X					X			
	D-RFS	X	X	X	X	X					X			
	RFS	X	X	X	X	X	X	X	X		X		X	
	L-RFS	X	X	X	X	X	X	X	X				X	
	RFi	X					X	X	X		X		X	
	BCFi	X					X	X	X	X	X		X	X
	D-RFi	X									X			
Metastatic	PFS	X	X	X	X	X	NA	NA	X		X			
	TTP	X					NA	NA	X		X			

It was recommended not to include the following events in any of the time-to-event end points: loss to follow-up.
BCSS, breast cancer-specific survival; iDFS, invasive disease-free survival; D-DFS, distant disease-free survival; D-RFS, distant relapse-free survival; RFS, relapse-free survival; L-RFS, locoregional relapse-free survival; RFi, recurrence-free interval; BCFi, breast cancer-free interval; D-RFi, distant recurrence-free interval; PFS, progression-free survival; TTP, time-to-progression; NC, no consensus.

Breast cancer

Gourgou-Bourgade et al. Annals Oncol. 2015

Table 2. Nonmetastatic setting: results of first and second rounds, face-to-face meeting

Event	End point						
	1. KCSS	2. DFS	3. RFS	4. MFS	5. LRFS	6. LGFS	7. FFS
Contralateral kidney cancer	NO	IN-2	IN-2	NO	O-2	TO	IN-2
Appearance of metastases	TO	IN-1	IN-1	IN-1	O-2	O-2	n/a
Local recurrence	TO	IN-1	IN-1	TO	IN-1	IN-1	n/a
Regional recurrence	TO	IN-1	IN-1	TI	TI	IN-1	n/a
Second primary invasive cancer (nonkidney)	O-1	TO	O-1	O-1	O-1	O-1	n/a
Local progression	TO	n/a	n/a	n/a	n/a	n/a	IN-1
Regional progression	TO	n/a	n/a	n/a	n/a	n/a	IN-1
Progression of metastases	TO	n/a	n/a	n/a	n/a	n/a	IN-1
Death from kidney cancer	IN-1	IN-1	IN-2	IN-2	IN-2	IN-2	IN-1
Death related to a second cancer	O-1	TI	TO	TO	TO	TO	NO
Death from nonkidney cancer cause	O-1	TO	TO	TO	TO	TO	TO
Death related to protocol treatment	TI	IN-2	NO	TO	TO	NO	IN-2
Death from any cause	TO	NO	NO	TO	TO	TO	NO
Death from unknown cause	TO	TI	NO	NO	NO	TO	TI

NO, no consensus; IN-1, include event first round; O-1, exclude event first round; IN-2, include event second round; O-2, exclude event second round; TI, tendency to include during face-to-face meeting; TO, tendency to exclude during face-to face meeting; n/a, not applicable. End points: 1. KCSS, kidney cancer-specific survival; 2. DFS, disease-free survival; 3. RFS, relapse-free survival; 4. MFS, metastasis-free survival; 5. LRFS, local recurrence-free survival; 6. LGFS, local regional-free survival; 7. FFS, failure-free survival.

Renal cell cancer

Kramar et al. Annals Oncol. 2015

DATECAN-1

- Guidelines
  - Available for various cancer sites
  - Ongoing for additional cancer sites
    - Head and neck cancer
    - Stomach cancer
    - Colorectal cancer
    - Lung cancer
- Further issues – further research
  - Need to collect information in CRF
  - Measurement issues
  - Constant update
  - Dissemination & diffusion

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Surrogate assessment in cancer trials

DATECAN-2 project

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Rationale

- Standardized definitions of endpoints available
  - Sarcomas and GIST
  - Breast cancer
  - Pancreatic cancer

- Next questions
  1. What is the impact of using various definitions for the same endpoint

     Ongoing work

  2. Can we use these endpoints as primary endpoints ?
     - Surrogacy - Ongoing work (Communication tomorrow : M. Savina)
       - Review of available studie assessing surrogacy
       - Sarcoma / GIST
       - Adjuvant breast cancer
       - Pancreatic cancer

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Endpoints for cancer trials in elderly patients

DATECAN-Elderly project

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Rationale (1)

- Overall Survival (OS)
  - Gold standard in randomized controlled trials (RCTs)
  - Evaluation of treatment efficacy

- OS in the elderly: Limitations
  - Competing risks: Death related to non-cancer causes
  - OS : relevant endpoint ?
    - Primary interest: Quality of Life (QoL), autonomy
    - Tumour-centered or patient-centered outcome ?

- Heterogeneity of primary endpoints used in RCTs (SIOG/EORTC)
- No recommendations available for use / definition

Wildiers et al. J Clin Oncol 2013 ; Pallis et al. Annals Oncol 2011

Rationale (2)

- Census of French trials 1998 – 2015 in geriatric oncology

Primary endpoint distribution (n=102 trials)		
Cancer related N = 64 trials (63%)	**Geriatrics N = 27 trials (27%)**	**Other N = 20 trials (20%)**
Survival: OS Anti-tumoral activity: PFS, EFS, etc. Safety	Quality of Life Autonomy Functional Status Cognition Nutrition Social support	Treatment feasibility Observance Biology

Type of primary endpoint	
Composites n=54 (59.3%)	**Co-primary n=10 (11%)**
Tumoral/Response duration	Tumoral + functional status
Tolerance	Tolerance/QoL
Tumoral/Survival	Survival/QoL

Rationale (3)

- Heterogeneity
  - Various definitions for a given endpoint
  - Nature of the primary endpoint

    Tumor centered / patient centered
  - Type of the primary endpoint

    Single primary endpoint / co-primary / composite

→ Difficulty when interpreting trials' results + design of future trials

→ Need for standardization of endpoints

DATECAN-Elderly: Objective

- Elaboration of guidelines for the standardization of definitions for endpoints to be used in cancer trials in elderly cancer patients
  - Ongoing review of published trials / endpoints commonly used in elderly cancer patients
  - Consensus process to be launched – same methodology
    - Mutlidisciplinary panel
    - International experts (SIOG, EORTC)
    - Expected results 2018-2019

DATECAN initiative

- Guidelines
  - Available for various cancer sites
  - Ongoing for additional cancer sites + specific population
- Diffusion of guidelines should help …
  - standardize assessment of future treatments
  - Comparison of future trials
  - Design of future trials
- Still several issues
  - Measurement issues
  - Constant update
- Success story / successfull collaborative & international research

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Thank you for your attention

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The DATECAN initiative

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et al.

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Back-up slides

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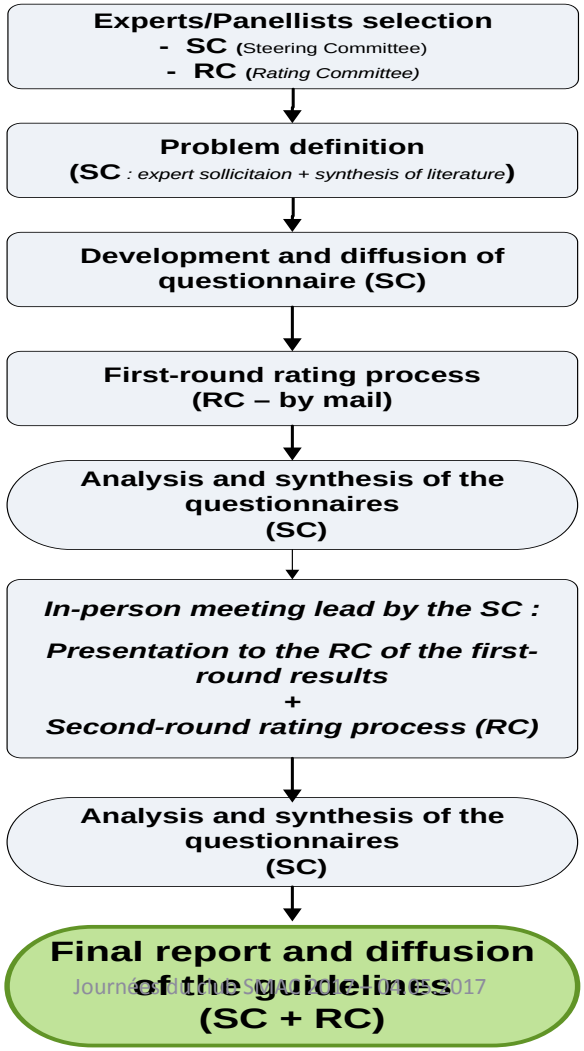
DATECAN-1: consensus process



Formal Consensus Method
(« RAND appropriateness method » as proposed by Rand Corp. And UCLA)

For each cancer site

SC : Steering Committee
RC : Rating Committee

DATECAN-1: scoring process

- **After the 1st scoring round,** consensus is reached if one of the following conditions is satisfied :
  1. The **median** of all scores lies in **{7, 8, 9}, and so do the minimum and maximum scores** (thus all scores are in {7,8,9}**).** In such case, there is strong consensus for including this event in the endpoint definition.
  2. The **median** of all scores lies in **{1, 2, 3}, and so do the minimum and maximum scores** (thus all scores are in {1,2,3}**).** In such case, there is strong consensus for excluding this event in the endpoint definition
- **In all other cases, the method considers that there was no consensus and a 2nd round of scoring is required.**
- **Please note that it is important that you score ALL items for which no consensus was reached at the 1st round. Indeed, by definition, the presence of two or more missing scores prevents reaching a consensus**