III – 4. TERMS AND CONCEPTS OF METHODS OF STUDY

See note opening section II – 2.

*Blinding** – In the methodology of a study, an arrangement making the observers unaware of certain facts (that might bias their observations); also: the counterpart of this in respect to the study subjects (notably as to the category of intervention to which they were assigned in an intervention-prognostic study, so as to prevent this influencing their engagement in extraneous interventions and/or their reporting on their experiences).

Note: If both the observers and subjects in a study are blinded, the study is said to be *double-blinded*.

*Blocking** (synonym: restriction of randomization) – In the randomization of (allocations in) an experimental intervention-prognostic study (randomized trial), the feature of the randomization being performed separately within subsets – component 'blocks' – of the study subjects with the same allocation ratio(s) in all of these. (Cf. 'Randomization.')

Note: Blocking fully assures the balance (at T_0) in respect to the blocking factor, while randomization assures it only stochastically.

*Clinical trial** (synonyms: randomized trial, randomized controlled trial) – An intervention-prognostic experiment for clinical medicine. See 'Randomized controlled trial.'

Note: The term is a bit of an euphemism, to avoid the unpleasant connotations commonly associated with 'experiment' when the subjects are humans. The term is a cognate of 'trying,' used in reference to intervention in clinical practice, free of any untoward connotations.

*Cochrane collaboration** – "An international organization of clinicians, epidemiologists, patients, and others that aims to help health professional to make well-informed decisions about health care by preparing, maintaining, disseminating, and promoting the necessary systematic reviews of the effects of health care interventions. *Cochrane Reviews* are prepared and updated by collaborating authors working in a *Cochrane Collaborative Review Group* and using explicity defined methods to

O. S. Miettinen, *Epidemiological Research: Terms and Concepts*,
DOI 10.1007/978-94-007-1171-6_11, © Springer Science+Business Media B.V. 2011

minimize the effects of bias; where appropriate and feasible, meta-analysis is used to reduce imprecision" [4].

Complete randomization (antonym: restricted randomization) – Randomization of (allocations in) an experimental intervention-prognostic study (randomized trial) performed without any restriction by way of randomized blocks. See 'Randomization' (Note 1).

*Compliance** – A misnomer for a study subject's – study population member's – adherence to what (s)he presumably is committed to per 'informed consent.'

Note: Compliance really means subordination/submission to an order. 'Compliance' in the meaning here should be replaced by 'adherence.'

Conclusion – See sections I – 2. 2 and II – 4.

*Confidence interval** – Misnomer for *imprecision* interval for a/the result of a study. (Cf. section II – 4.)

*Confounding by indication** – In an intervention study, confounding by the indication for the intervention (as is obvious from the term).

Note 1: One of the major differences between etiogenetic and intervention studies, on the level of the object of study already, is that the former are generally about unintended effects, while the latter are mostly about *intended* effects [9]; and since the indication for intervention generally is an indication of the (prospective) outcome the risk of which is intended to be reduced by the intervention, the *indication is an inherent – ubiquitous – confounder* in the intervention versus no intervention contrast and a common possibility in inter-intervention contrasts as well [62, 63]. When the details of the indication are not subject to close documentation (for control of the confounding), the need is to *prevent* confounding by it – by resorting to experimentation with *randomization* as the basis for intervention allocation [62, 63].

Note 2: Confounding by indication is commonly mistaken to be a form of selection bias (instead of confounding bias). But it is not bias of any form (in the study result); it is only a *potential source of confounding bias* – which confounding is to be prevented if it cannot be controlled.

Note 3: Very distinct from confounding by indication is confounding by contra-indication [62, 63] – contra-indication generally being, if present at all, (1) very rare rather than ubiquitous, among the study subjects; (2) without inherent status as a determinant even of the unintended, rare outcomes that may be addressed (with generally quite wanting precision); and (3) generally quite readily subject to documentation.

Note 4: Significantly, the I.E.A. dictionary [4] writes about confounding by indication with a reference only to the Editor himself, in 1998; and it is presented not as "a type of confounding" but of "confounding bias," and it is equated with bias from contra-indication, adding that "It shares some features with 'susceptibility bias,' 'procedure selection bias,' 'protopathic bias,' and 'selection bias.' "

*Consent** – A person's agreement to submit to simulated care (diagnostic or interventive, in an experiment) and to the use of the data for research; or, to the use of the data on actual care for research.

Note 1: Ethics requires the consent to be *informed* – meaning well-informed, first as to the (true) implications, to the consenting person, of the consent relative to not consenting. An added meaning of well-informed consent is that the consenting person is made aware of the (true) motives for the solicitation of the consent (pecuniary, careerist, or whatever other self-serving motives first and foremost). For, a doctor is ethically bound to act in the best interest only of the client (as a matter of the unspoken 'fiducial contract' between them).

Note 2: *Equipoise** – "A state of genuine uncertainty about the genuine benefits or [*sic*] harms that may result from different exposures or interventions . . . [it] is an indication for a randomized controlled trial" [4], meaning that it gives an ethical warrant for soliciting participation in an RCT. But the question is, Whose equipoise? the investigators'? The answer: For the solicitation, a first ethical requirement is that the potential participant be *compos mentis*, and that in the view of the relevant *scientific community* at large, there could be *potential study subjects* who, once (truly) well-informed and also compos mentis, would be willing to participate. And a well-informed person's decision to participate is not predicated on his/her equipoise. (S)he may wish to contribute to relevant research even with some perceived risk to his/her own health.

Note 3: In today's IRB-approved experiments (diagnostic or interventive) on human subjects, the solicitation of purportedly informed consent is, quite routinely, disingenuous. A telling indication of this is that, quite routinely, the information given out in the solicitation is intentionally kept unchanging throughout the period of subject accrual – deliberately excluding from it the evidence garnered in the study itself and, also, evidence from other simultaneously on-going similar studies.

Note 4: Apart from the requirement of obtaining informed consent, ethics of human experimentation is now taken to involve the work of a *Data Safety and Monitoring Board*, "charged with assessing the progress of clinical trials and to recommend whether the trial should continue, be modified, or be discontinued. More specifically, the DSMB approves the protocol, . . . ; and DSMBs review interim analyses . . . performed prior to study completion" [64].

Note 5: If the trial participants were (truly) well-informed, not only at enrolment but in the course of their trial participations also, there would be *no need, nor justification, for DSMBs* to take decisions about trials' continuations/stoppings. The participants would, individually, take the decisions; and stoppings by DSMB decisions would thus be replaced by vanishing of the continually participating volunteers.

Note 6: Even though the language here focuses on trials in clinical research, epidemiologists in their research for community medicine also engage in trials with individuals as the units of observation. Examples: trials on screening for a cancer, trials on chemoprevention of cancer, and trials on vaccinations – recently including vaccination in the prevention of cervical cancer.

Note 7: While an individual's enrolment into participation in a health-related study – non-experimental study included – is generally supposed to require, as a matter of ethics, the individual's informed consent, in many jurisdictions cancer patients are legally obligated to provide data for cancer research (by cancer registries). Operative in this can be said to be not *deontological* but *teleological* – utilitarian – ethics, the creed which, in the words of J. S. Mill, "accepts as the foundation of morality, Utility of the Greatest Happiness of People" [65]. Deontological (duty-based) ethics is supposed to be the sole concern in clinical research, but a more natural ethical stance in community research can be seen to be the teleological (goals-oriented) one, though with due respect for individual values (re personal happiness).

*Contamination** – In a randomized trial, non-adherence to the assigned category of intervention in the form of crossing over to an/the other category (irrespective of whether at issue is the study subject's or the investigators' non-adherence to the trial's protocol).

Note 1: 'Contamination' in reference to protocol non-adherence is as ugly a term as is 'discharge' for the termination of hospitalization.

Note 2: There really is no genuine need for a term specific to intervention crossover as a particular subtype of protocol non-adherence in an intervention trial, one that distinguishes this from other, equally deleterious types of non-adherence to the intervention protocol.

*Control** – See 'Randomized controlled trial' (Note 2).

Data Safety and Monitoring Board – See 'Consent' (Note 4).

Diagnostic study – The structure ('architecture') dictated by logic for any study intended to serve advancement of the (scientific) knowledge-base of diagnostication (i.e., of setting diagnostic probability for the presence of the illness at issue). Its elements are: (1) study base constituted by a series of person-moments from the domain of diagnosis (chief complaint, . . .); and (2) for the study base, documented counterpart of the (designed) object of study (diagnostic probability function – logistic).

Note 1: Always to be reported is the result without shrinkage; but the result with shrinkage also needs to be derived and reported whenever at issue is the first study (original or derivative) on the object function and the result might be applied as such (without its translation to knowledge; cf. 'Gnostic expert paneling').

Note 2: A diagnostic study, in this sense, may address a test's informativeness in the sense of producing both a pre-test and a post-test DPF, thereby providing for studying the test's *informativeness* (see 'Diagnostic test's properties' in sect. III – 3). In such a study, a measure of this could be $I = 1 - R^2$, R being the 'coefficient' of correlation between the pre- and post-test probabilities. ($R^2 = 1$ means $I = 0$, complete uninformativeness of the test result.)

Note 3: Study of a test's *informativeness* preferably has a different object of study, one not focusing on DPFs. The dependent variate does not signify the presence/absence of the illness but, instead, whether the post-test probability falls in a particular range; and the object of (each component) study is the probability of this as a function of the pre-test indicators. (See 'Diagnostic test's properties,' Notes 3 and 4, in sect. III – 3.)

*Double blinding** – See 'Blinding' (Note).

Endpoint – In a prognostic study (RCT, say), the point at which follow-up ends on account of the outcome event occurring.

*Equipoise** – See 'Consent' (Note 2).

*Ethics** – See 'Consent' (Note 7) and 'Institutional Review Board' (Note 1).

Etiognostic study – The structure ('architecture') dictated by logic for any study of etiogenesis, intended to serve advancement of the (scientific) knowledge-base of etiognostication (i.e., of setting probability for causal – etiogenetic – role for an antecedent of an illness). The structure is the general one of an etiologic/etiogenetic study. (Special is only the stage of the evolution of the knowledge – in which quantification has come to follow hypothesis-testing – and the richness of detail in the occurrence relation needed for clinical etiognosis.)

Expert – A gnostician who, in dealing with cases from the domain at issue, is judged (by colleagues) to be as competent as anyone.

Note 1: At present, an expert's competence in setting gnostic probabilities is, quite exclusively, a matter of *tacit* knowledge in particular cases that come up – knowledge accrued largely on the basis of *personal experience* with cases from the presentation domain at issue. It thus is not knowledge derived – collectively – from quintessentially applied clinical research (via gnostic expert paneling).

Note 2: In the now-foreseeable future, it will be generally understood that (1) the knowledge-base of clinical medicine can be – and needs to be – codified in the form of gnostic probability functions; and that (2) quasi-scientific GPFs, representing experts' tacit knowledge without inputs from research on the GPFs, can be developed quite rapidly and inexpensively, without having to await the results of (the still essentially non-existent) research on GPFs. Given this understanding – and the ever-mounting pressures of quality-assurance and cost-containment – clinical gnosticians in general will, in the foreseeable future already, function like experts typically do, their practices guided by *gnostic expert systems* [16].

Note 3: As research on GPFs gets underway in earnest, true understanding of such research becomes an important added element in the competence of expert gnosticians in the various disciplines ('specialties') of clinical medicine.

Gnostic expert paneling – Translation of evidence into practice-guiding knowledge about a gnostic probability function: A panel of experts (on the gnosis at issue)

are presented with vignettes (scores of them) of hypothetical patients, each profile supplemented by the value implied by the relevant study result (if available); the panel members specify, independently, their perception of the gnostic probability in each of the (hypothetical) cases, and the median of these probabilities is derived for each case; these medians are translated into the corresponding GPF by fitting it to the data, both without and with shrinkage [16].

*Goodness of fit** – Concerning the result of regression 'analysis,' the extent to which the observed means of the dependent variate conform to the respective 'estimates' from the empirical (fitted) regression function across various ranges of the 'estimates' (in a diagnostic study, say.)

*Hawthorne effect** – In experiments on human subjects (RCTs, say), the study subjects' changes of behavior not intended by the investigators yet consequential to the study outcome(s).

Note: The effect fundamentally is that of increased health-consciousness, and its consequent changes of behavior generally are intended to change the course of health for the better (by actions that are extraneous from the vantage of the experiment). To the extent that the Hawthorne effect is there in a consequential way, the prognostic results of RCTs conditional on the choice of intervention tend to have a bias toward more favorable outcome(s).

Hierarchy of evidence – See section II – 4.

*Informed consent** – See 'Consent' (Note 1).

*Institutional Review Board** – In the U. S., the committee each research institution is required to have for evaluation of each plan, in the institution, for a study that would involve human subjects. The IRB is to pass judgment about whether the study would be ethical and, in this sense, admissible.

Note 1: For a study involving human subjects to be ethically admissible, it is to satisfy the imperatives of both teleological and deontological ethics. *Teleologically*, the study – like any other action/activity of humans – is (to be intended) to enhance the aggregate happiness of mankind (i.e., to have utility – positive – from this 'mass' perspective); and *deontologically*, it must not impose on the study subjects any disutility (suffering or deprivation) that teleologically is uncalled for and/or is unacceptable to the study subjects – compos mentis and, in relevant respects, fully informed. (Gr. *teleos*, 'complete, final'; Gr. *deon*, 'binding, needful.')

Note 2: An IRB – this 'ethical' committee – acts unethically if it approves a study without full assurance – full knowledge – that the study actually is ethically admissible; and an IRB makes this ethical error most generally and most fundamentally by presuming to be qualified to pass ethical judgments on whatever study involving human subjects. For, such a study is unethical – an unethical imposition on the study subjects – if it is wanting in quality-optimization of its object(s) and/or methods designs, including in maximization of the study's efficiency; and it

is unethical if the 'informed consent' is sought without making the study subjects truly fully-informed. See 'Consent.'

Note 3: The elements in this quality-optimization in this information-transmission are matters of extra-ethical expertise and inter-institutional in nature; and thus, the only justifiable, truly ethical role for an IRB really is making sure that genuine expertise on these matters has been brought to bear on, and heeded, in the design of the study and of the consent form. For intra-institutionally, horrendous contraventions of research ethics can take place, even in ostensibly legitimate institutions, starting from the studies' object(s) designs [66]. And an IRB, however well-intentioned, generally is not qualified to judge the adequacy of the information input into the solicitation of informed consent for study participation – to act on behalf of the relevant scientific community in this judgment. (Cf. 'Consent.')

*Intention to treat** – In the result of an RCT, the quality that its referent is the contrast formed by the randomizations, regardless of whether the interventions actually conformed to the randomized assignments.

Note: The ITT quality of an RCT result implies freedom from confounding (systematic) at T_0 of prognostic time; but it implies bias on account of incompleteness (if any) of adherence to the randomly assigned interventions.

Intervention-prognostic study (synonym: intervention study) – See 'Intervention study.'

*Intervention study** (synonym: intervention-prognostic study) – The structure ('architecture') dictated by logic for any study on the intended effect(s) of an intervention. Its elements are: (1) the study base constituted by a segment (early) of the prospective course of a cohort, with subcohorts according to the contrasted interventions, this divergence prevailing as of cohort T_0 (but not before); and (2) for the study base, documented counterpart of the designed object of study.

Note 1: At present in RCTs, as for the implicit object of study, the effect of an intervention (relative to its alternative) is commonly addressed in terms of deriving from the data the 'hazard ratio' – meaning the empirical value of this parameter – together with the 95% 'confidence interval' to go with this. But, bringing the structure of the etiologic study (sect. II – 4) suitably to bear, an (empirical) prognostic probability function (of prognostic time, intervention, and prognostic indicators at cohort/prognostic T_0) can, and should, be derived from the data [9, 16] – upon suitable design of the form of this (in the study's object design). Rather than a mere intervention study, such a study is an *intervention-prognostic study*.

Note 2: While the structure of an intervention study has that of the RCT as its paradigm, an intervention study need not be experimental, to have experimental arrangement of the contrasted treatments. The structure can be *quasi-experimental* in its genesis (see sect. I – 2. 2).

Note 3: See also 'Prognostic study.'

IRB – Institutional Review Board.

*Kaplan-Meier-Greenwood statistics** – The Kaplan-Meier 'point estimate' together with the Greenwood standard error for the complement of cumulative incidence in the time-course of a cohort (with terminations of follow-up also for reasons other than the event at issue).

Note 1: When at issue is *survival* in a cohort of patients diagnosed with a particular illness (cancer, notably), the K-M 'estimate' represents the cohort's rate of surviving the illness at issue for a given period of time since cohort T_0 in the absence of deaths from other causes – that is, when (counterfactually) regarding the illness at issue as the only cause of death.

Note 2: The *K-M survival rate* [67] is derived by focusing, in the cohort's follow-up time, on the points at which deaths from the cause/illness at issue occur. When the first (known) death from this cause occurred, the number of survivors under follow-up changed from S_1 to $S_1 - 1$, and the survival rate became $(S_1 - 1)/S_1$. If, in the follow-up period at issue, a total of d deaths from the cause at issue occurred, the K-M survival rate was the product of d proportions of this type:

$$R = \prod_1^d (S_i - 1)/S_i (i = 1, \ldots, d).$$

This rate is, thus, derived without any regard for the numbers of losses to follow-up as well as of deaths from other causes in the time period at issue, including in the subperiod of time after the last death from the cause at issue (in which period the size of the subcohort still under follow-up may have declined to however meaningless a number).

Note 3: The Greenwood standard error for the K-M survival rate (R) is [69]

$$SE = R\left[\sum_1^d 1/S_i(S_i - 1)\right]^{1/2}.$$

Involved in this is ML estimation of the binomial variances. Based on the corresponding unbiased estimates, the counterpart of this is [68]

$$SE = R\left[\sum_1^d 1/(S_i - 1)^2\right]^{1/2}.$$

(In general, unbiased 'estimates' are used and preferred. This tends to be forgotten in the context of the readily obtained ML values for the Bernoulli and binomial variances.)

Note 4: The complement of the K-M survival rate a modern epidemiologist naturally thinks of as the *cumulative incidence-rate* of death from the illness at issue in the time period at issue. Like the K-M survival rate, this CIR is conditional on not succumbing to a 'competing' cause of death (as it is based on incidence density of the death at issue, inherently among survivors). Specifically, with the survival period divided into a set of subperiods, and with d_j deaths from the cause at issue occurring in the j^{th} subperiod of duration t_j and population-time T_j of follow-up, the complement of the K-M survival rate can be derived as [69]

$$\mathrm{CIR} = 1 - \exp\left[\sum_j (d_j/T_j)t_j\right].$$

This generally is in close agreement with the K-M survival rate.

Note 5: The SE relevant to this CIR is that of the time-integral of incidence density (in the exponential). This is:

$$\mathrm{SE} = \left[\sum_j d_j(t_j/T_j)^2\right]^{1/2}.$$

With this SE applied to the exponent in the CIR, 'confidence' limits for the theoretical CIR are, generally, in close accord with the complements of the K-M-G limits.

Note 6: SE-based limits are not first-principles limits. In the case at issue here, they are not, even, inherently bound to remain within the 0-to-1 range. The CIR approach, however, lends itself to derivation of first-principles limits, and not only asymptotic limits (like these SE-based ones) but 'exact' ones as well [69].

Note 7: An eminent alternative to the K-M survival rate is the *Nelson-Aalen* 'estimator,'

$$R = \sum_1^d 1/S_i;$$

but preferable to this can be taken to be [69]

$$R = \sum_1^d 1/(S_i - 1/2).$$

Likelihood – A misnomer in reference to a study result when saying that one group had a higher, or lower, 'likelihood' of the outcome when at issue is merely an empirical difference between two rates. (Cf. 'Result' in sect. II – 4.)

*Meta-analysis** – In a derivative study, synthesis of the results of original studies.

Note: The term is a misnomer. For one, the 'analysis' actually is synthesis (cf. 'Analysis and synthesis' in sect. I – 2. 2). For another, at issue still is 'analysis,' rather than something that transcends it. (Cf. 'meta-physics.')

*Overparametrization/overfitting** – See section III – 3.

Prognostic study – The structure ('architecture') dictated by logic for any study of the course of health, intended to serve advancement of the (scientific) knowledge base of prognostication. Its elements are: (1) study population constituted by a cohort whose members are enrolled from the domain of the prognostication; (2) study base constituted by the study cohort's prospective course (in cohort and prognostic time); and (3) for the study base, the documented counterpart of the (designed) object of study (prognostic probability function).

Note 1: The prime generic example of a prognostic study is the *randomized controlled trial* (of interventions) addressing a prognostic probability function.

Note 2: For documentation of a PPF for a *state* of health, contributions to the study base are not terminated by 'endpoint' events. A sample – in principle any type of outcome-independent sample (finite) – of the (infinite number of) person-moments of the study base is selected and documented, and the PPF is fitted to these data – without and with shrinkage. The state of health at a given time may be the then frequency of episodes of sickness from the illness (epilepsy, say) – the then moving average of this frequency.

Note 3: For documentation of a PPF for an *event* of health, contributions to the study base are terminated by the event's occurrence. Regarding the event, the case series is identified and documented in respect to intervention history (type of intervention and time since cohort/prognostic T_0) and prognostic profile at T_0. The case series is supplemented by a base series, selected as a *representative* (simple random) sample of the study base and documented analogously with the case series. The logistic counterpart of the log-linear model for the event's incidence density (as a function of prognostic time, choice of intervention, and prognostic indicators) is fitted to the data on these two series. The result for the event's incidence density is the fitted logistic function's exponential multiplied by b / B, where b is the size of the base series and B is the amount of population-time constituting the study base. The integral of this function over prognostic time is translated into its corresponding cumulative incidence and, thereby, to the result for the prognostic probability function [9].

*Randomization** – Random assignment/allocation of study subjects to particular ones of the compared/contrasted interventions.

Note 1: In *complete* randomization, all of the allocations are mutually independent, except for the possible role of a preset allocation ratio.

Note 2: In *restricted* randomization, a given allocation ratio is designed to be the result of randomization within defined 'blocks' of study subjects (patients from a particular participating clinic, say), but among the blocks the randomizations are mutually independent.

*Randomized controlled trial** (synonyms: randomized trial, clinical trial) – An experimental intervention-study, one in which the allocations to the contrasted interventions are based on randomization.

Note 1: An RCT is usually a *parallel* trial, one with treatment-specific subcohorts formed and then followed in parallel in calendar time. But an alternative to this is a *cross-over trial*, in which the study subjects change from one of the contrasted treatments to the other one in the course of their follow-up. This type of trial, too, can be randomized, now in defining the individual sequences in the use of the contrasted interventions.

Note 2: The meaning of '*control*' in this context is not that there is experimental control of the allocations to the contrasted interventions; this is the meaning of 'trial' (i.e., 'experiment'). Instead, the meaning is this: In studying the effect(s) of a particular intervention, experience with a cohort subjected to this intervention shows only what happens with this intervention; the experience does not show what would

have happened without this intervention. To learn about the latter, a 'control' cohort subjected to the intervention's alternative is included in the trial.

Note 3: The term '*trial*' in this context is a bit of an euphemism (cf. Note under 'Clinical trial'). And once a trial is *randomized*, it inherently also is controlled (in the meaning of Note 2 above), so that '*randomized trial*' should be preferred over 'randomized controlled trial' as the term for this type of clinical study.

Randomized trial (synonyms: randomized controlled trial, clinical trial) – See 'Randomized controlled trial' (Note 3).

RCT – Randomized controlled trial.

RCTism – The doctrinary outlook in terms of which even diagnostic testing is intervention (on the course of health), intended to have efficacy/effectiveness, and thus is to be assessed by means of RCTs. (Cf. 'Outcomes research' in sect. III – 2.)

Reduction – A misnomer for a result consistent with a reducing effect.

Note: The word derives from a transitive verb. It has to do with causation (a noumenon) which the difference or ratio does not inherently represent.

*Regression toward the mean** – The tendency of a repeat observation (with chance error) to be closer to the mean.

*Replication** – Concerning a measurement, its repetition with a view to reduction of chance error in the result; also: concerning an object of study, conducting a new study on it with the essentials of design and protocol as in a previous study on it – though in a different place at a different time and, generally, with a different precision (on account of different efficiency and/or size) – with a view to potential corroboration. (Cf. sect. I – 2. 2.)

Restricted randomization – See 'Randomization' (Note 2).

*Sample size determination** – See section II – 4.

Note: 'Sample size determination' is outstanding among the negative contributions of statistics to statistical science. The most common statistical consultation for study design by clinicians concerns 'sample size determination.'

*Shrinkage** – In the context of 'overparametrization' of a regression model and its consequent 'overfitting' of the model (sect. III – 3), correction for the bias in the 'estimates' for the dependent parameter, resulting from the large number of parameters in the model in proportion to the number of units of observation in the study.

Note 1: 'Overparametrization' is a misnomer in this context, and so also is 'overfitting.' 'Overparametrization' properly refers to a flaw in object design, for a diagnostic study in particular, and this is not what actually is at issue here. The

context of the diagnostic probability-setting is prone to involve dozens of diagnostic indicators, and a reasonable regression model even more independent parameters; and a biased result from the fitting of the model is not really a result of a flaw in the parametrization of the model nor in its fitting to the study data. The bias actually is a consequence of *undersizing* of the study – insufficient number of units of observation in proportion to the number of parameters in the model. (Cf. sect. III – 3.)

Note 2: The nature of the bias is unusual, given that the 'estimates' for the dependent parameter from the fitted 'polymultiple' regression have no systematic error in the usual, across-the-board meaning. Instead, the resulting relatively low 'estimates' involve a downward bias, the relatively high ones an upward bias. This result-specific bias arises from the fact that, in the database, the relatively low values of the dependent variate are prone to involve a negative 'error' (chance element), the relatively high values a positive one – and the fitting of the polymultiple regression model traces these patterns of chance in addition to reflecting the actual values of the parameters in the model.

Note 3: This extraordinary type of bias – a feature not of the fitted coefficients but of the linear compound of these, when viewed as the empirical value of the dependent parameter conditional on the (polymultiple) set of independent variates – has the extraordinary character that it is reduced – and ultimately eliminated – by increasing size of the database, as in moving from an original study to a derivative study drawing from several original studies. Thus, correction for the bias – shrinkage, that is – is called for only insofar as the result, whether from the first original study or a subsequent derivative study, will be applied as such – before bias-reduction from further contributions to the aggregate of evidence (about the magnitudes of the model's independent parameters).

Note 4: Among the various available ways of effecting the requisite shrinkage, the most intuitive one arguably is the '*leave-out-one*' method: Of the N datapoints, one is left out in fitting the model (to the other N−1), and this fitted model is used to derive the value $\hat{Y}_1$ corresponding to the left-out value Y_1. This process is repeated for each of the other datapoints, leading to data pairs $(Y_i, \hat{Y}_i), i = 1, 2, \ldots, N$. In the usual context of the regression model being logistic, the next phase is to fit a univariate regression model for the mean of the logit of Y, involving $B_0 + B_1 X$, where X is the logit of the 'estimate' based on the fitting without shrinkage. In this, the need for shrinkage is manifest in $\hat{B}_1 < 1$. Finally, then, the result with the requisite shrinkage is, for the logit of the mean (P) of Y, incorporated in $\hat{B}_0 + \hat{B}_1 L$, where L is the linear compound from the initial fitting – 'overfitting' of the polymultiple regression model (requiring shrinkage by the factor $\hat{B}_1$).

*Survival analysis** – See 'Kaplan-Meier-Greenwood statistics.'

*Systematic review** – A review of and report on all original studies on the object at issue, especially if 'meta-analysis' is involved.