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Research Article

INFORMED CONSENT STATUS IN OBSERVATIONAL STUDIES WITH RETROSPECTIVE DESIGN: A POOR SHOW

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ABSTRACT

Objective: Informed consent is very important to protect the rights of patients and is obtained as a vital component of any clinical study. Requirement of patient consent in retrospective research continues to stir controversy even today. Some of directions of regulatory authorities even waive off the consent for retrospective studies, whereas few recommend that at least clearance from the Ethical Review Board may be taken or information to patient may be given or oral consent must be given by patient for usage of the data in any retrospective study. The aim of this study was to analyze the current status of informed consent procedures in observational studies with retrospective design.

Methods: This review was intended to find out the current status of procedures involved in informed consent in India and abroad. A total of 100 retrospective studies were searched for this objective from the internet and other literature sources.

Results: Data show that in 65% of studies neither informed consent/oral consent nor ethical clearance was taken. Only 1% of studies have been conducted with informed consent as well as ethical clearance. Only 14% of studies were conducted with informed consent and 21% with ethical approval.

Conclusion: The study reflects very poor status of informed consent in retrospective studies and noncompliance of ICH guidelines for clinical research in relation to informed consent.

Keywords: Clinical research, Informed consent, Retrospective studies.

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INTRODUCTION

India has emerged as one of the preferred destinations for clinical trials of drugs by multinational pharmaceutical companies in recent years [1]. Quality of clinical trials relies on data consistency and subject safety. Ideally, all clinical trial ought to have a clinical trial quality management plan describing the tools that will be used to guarantee study quality. The adoption of quality-by-design and quality risk management methods for clinical trial management is the current mantra at Food and Drug Administration [2]. Retrospective clinical studies contribute a significant role in discovery or confirmation of important facts related to medicine. The issue of informed consent from participants has never been taken seriously by researchers for creating skewness in data resulting in the loss of important results [3,4]. Such skewness apprehends the researchers for exemption from need of informed consent. This finally makes the project leaders to overlook the basic ethics of informed consent and makes it further important for approval of an Institutional Ethics Committee (IEC). In general, patients may not be aware of use of data related to their ailment for other purposes and may feel offended as well as disappointed leading to loss of faith of their physicians. The risk further increases if the data are transferred to a third party not related with research group. As a matter of fact the usage of any data related to a subject in biobanks [5] and retrospective research (as explained in the international research guidelines of the Council for International Organizations of Medical Sciences [CIOMS]; commentary on guideline 4) can be used only with consent of the concerned subjects [6]. Informed consent enables a subject to adjudicate the pros and cons of the proposed medical treatment for final acceptance or refusal. This avoids or decreases the chances of errors, negligence, coercion, deception, and encourages the doctor's self-criticism. Informed consent is necessary in all studies of medical records and for use of sensitive personal information for research purposes.

Although as per memorandum of agreement in most countries, retrospective and epidemiological research is exempted from informed consent subject to preapproval by IEC, yet the scientific manipulations may easily find their way through ethics committees. According to Nuremberg Code 1949, informed consent must be obtained and is investigator's responsibility and no investigators should initiate epidemiological research involving human subjects without consent from subjects and a clear cut approval from legislation or competent authorities such as an Ethical Review Committee. Consent may be obtained in any way like voluntary actions, oral consent, signing a consent form. In the case of incompetence of the subject, a duly authorized representative should do so. Although in some communities, the family head is considered to give the consent but then also the voluntarily consent from the subject participating in the research is must. In addition in case of the minimal risk, ethical review committee may approve waiver of the requirement of a signed consent form. Such waivers may also be applied in case of unjustified threat to the subject's confidentiality.

Many bioethicists [7] and the Swiss Academy of Medical Sciences [8] opine that general consent in which patients receives information proportionate to the risks is sometimes sufficient. A broad consent to future research can be applied if these risks are low and patient may also refuse to provide general consent, and instead stipulate the use of data in only specific projects. Even for the research which involves the minimal risks to the patients or does not have any direct relation

with the patients prior informed consent may be avoided however to ensure ethical importance of treating people with respect, information regarding right to leave the study should be clearly conveyed. It has been observed that researchers do not give much attention to this issue and hurriedly finish the retrospective analysis without keeping in view the interest of subjects and play with the rules and regulations setup by regulatory bodies. Hence, it was pertinent to find out the exact current status of informed consent procedures. The purpose of this study was to find out the current status of informed consent in observational studies with retrospective design in India and abroad.

METHODS

A total of 100 such observational studies with retrospective design involving 2,346,261 patients (Table 1) were reviewed from the internet and other literature resources. The status of the informed consent was

Table 1: Data showing name of retrospective study along with consent taken, number of subjects, and material use in retrospective studies

S.No.	Title of the study/reference	Informed consent	Number of subjects	Material used for study
1	Retrospective study in breast cancer patients supplemented with AHCC [10]	No	58	Medical records
2	A retrospective study on pathologic features and racial disparities in prostate cancer [11]	No	3000	Pathology reports
3	Are antinuclear antibodies useful in neurologic patients? A retrospective analysis based on 545 cases [12]	No	545	Laboratory reports
4	Tobacco habits and risk of oral cancer: A retrospective study in India [13]	Yes	520	Cancer registry
5	A retrospective study on patients with Guillain-Barré syndrome treated with therapeutic plasma exchange and other treatment options: A center's experience [14]	Yes	56	Medical records
6	Profile of neurological problems in diabetes mellitus: Retrospective analysis of data from 1294 patients [15]	No	1294	Medical records
7	Prognostic factors in cervical cancer: A hospital-based retrospective study from Visakhapatnam city, Andhra Pradesh [16]	No	552	Treatment records
8	Neurologic cytomegalovirus complications in patients with aids: Retrospective review of 13 cases and review of the literature [17]	IEC	13	Laboratory records
9	Neurological complications after renal transplantation: A retrospective clinical study [18]	No	19	Medical records
10	Retrospective study of reasons for improved survival in patients with breast cancer in East Anglia: Earlier diagnosis or better treatment [19]	No	8630	Cancer registry
11	A retrospective observational study of the relationship between family history and survival from colorectal cancer [20]	No	10937	Cancer registry
12	A retrospective study of gastric cancers in Tehran [21]	No	460	Pathology reports
13	Prevalence of inherited neurotransmitter disorders in patients with movement disorders and epilepsy: A retrospective cohort study [22]	IEC	154	Medical records
14	Etiologic spectrum of mental retardation and developmental delay in India [23]	No	338	Laboratory reports
15	Retrospective study of pulmonary hypertensive patients: Is right ventricular myocardial performance index a vital prognostic factor? [24]	No	93	Medical records
16	Changes in physical activity and travel behaviors in residents of a mixed-use development [25]	No	101	Subject's data
17	Anti-hypertensive prescribing patterns and cost analysis for primary hypertension: A retrospective study [26]	No	300	Prescription data
18	A cross-sectional retrospective study to assess the pattern of prescribing for inpatient hypertensive cases in a tertiary hospital and to find out the possible avenues for betterment of hypertension management [27]	IEC	261	Medical records
19	Prevalence and risk factors of HIV in Faisalabad, Pakistan: A retrospective study [28]	Yes	31040	Medical records
20	Vaccination of patients with diabetes mellitus: A retrospective study [29]	No	402	Medical records
21	The impact of multifactorial genetic disorders on critical illness insurance: A simulation study based on UK biobank [30]	No	500,000	Medical histories/blood samples
22	Major congenital anomalies: A five-year retrospective regional study in Turkey [31]	IEC	63,159	Medical records
23	A retrospective study of pulmonary tuberculosis (PTB) prevalence among patients attending infectious diseases hospital (IDH) in Kano, Nigeria [32]	No	3679	Laboratory reports
24	A retrospective study on incidence of pulmonary tuberculosis and human immunodeficiency virus co-infection among patients attending National Tuberculosis and Leprosy Control Program, Owo center [33]	No	342	Medical records
25	A retrospective study on the outcomes of tuberculosis treatment in Felege Hiwot Referral Hospital, Northwest Ethiopia [34]	IEC	756	Medical records
26	Prevalence of XDR TB cases – a retrospective study from a tertiary care TB hospital [35]	No	223	Laboratory reports
27	A retrospective study to determine the prevalence and outcome of tuberculosis among patients who visited the TB Annex Hospital in Congo Town, Monrovia, Liberia from July 2009 to July 2010 [36]	IEC	299	Medical records
28	Tuberculosis: An eight year (2000-2007) retrospective study at the University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia [37]	No	131	Medical records
29	Surgical safety checklist in obstetrics and gynecology [38]	No	185,000	Medical records

(*Contd...*)

Table 1: (*Continued*)

S.No.	Title of the study/reference	Informed consent	Number of subjects	Material used for study
30	Ectopic pregnancy and seasonal variation: A retrospective study from the South Western Region of Saudi Arabia [39]	No	21,564	Medical records
31	Comparison of survival and complication rates of tooth-supported fixed dental prostheses (FDPs) and implant-supported FDPs and single crowns (SCs) [40]	No	85	Internet/electronic search
32	A systematic review of the success of sinus floor elevation and survival of implants inserted in combination with sinus floor elevation [41]	No	12,020	Internet/electronic search
33	Timing of implant placement relative to tooth extraction [42]	No	10	Internet/electronic search
34	Photodynamic therapy as an adjunct to non-surgical periodontal treatment: A randomized, controlled clinical trial [43]	Yes	24	Treatment records
35	The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American association for the study of liver diseases, American College of Gastroenterology, and the American Gastroenterological Association [44]	No	26,527	Medical records
36	The outcomes of esophageal and gastric cancer treatments in a retrospective study, single center experience [45]	No	368	Medical records
37	Gastric cancer in women: A regional health-center seven year retrospective study [46]	Yes	285	Internet search
38	Clinical evaluation, prevalence and etiologic factors in patients with ophthalmoplegia [47]	Yes	226	Laboratory reports
39	Antipsychotic drugs and hyperglycemia in older patients with diabetes [48]	IEC	13,817	Prescription records
40	Spectrum of Celiac Disease at Tertiary Care Center of Northern India [49]	No	100	Pathology reports
41	Risk of cancer from occupational exposure to ionizing radiation: Retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS) [50]	No	308297	Medical records
42	Metformin use and lung cancer risk in patients with diabetes [51]	No	47,351	Medical records.
43	HIV and cancer: A comparative retrospective study of Brazilian and U.S. clinical cohort [52] (conducted in INI, 2925 patients and VCCC, 3927 patients)	Yes/No	2,925/3,927	Medical records.
44	Retrospective analysis evaluating ovarian cancer cases presented at the clinical oncology department, Alexandria University [53]	No	116	Cancer registry
45	Human papillomavirus (HPV) genome status and cervical cancer outcome: A retrospective study [54]	IEC	132	Medical records
46	Oral squamous cell carcinoma: A retrospective study of 740 cases in a Brazilian population [55]	No	740	Medical records
47	Neoadjuvant chemotherapy in advanced epithelial ovarian cancer: A retrospective study [56]	No	85	Medical records
48	Retrospective study of cancer types in different ethnic groups and genders at Karachi [57]	No	5134	Medical records
49	A new prognostic system for hepatocellular carcinoma: A retrospective study of 435 patients [58]	No	435	Laboratory reports
50	Timeliness of lung cancer care in Victoria: A retrospective cohort study [59]	IEC	1417	Cancer registry
51	Effect of neuraxial anesthesia on tumor progression in cervical cancer patients treated with brachytherapy: A retrospective cohort study [60]	IEC	132	Cancer registry
52	Pattern and trends of cancer in Odisha, India: A retrospective study [61]	No	74861	Cancer registry
53	Long term follow up and retrospective study on 533 gastric cancer cases [62]	Yes	533	Cancer registry
54	A retrospective study of the outcome of cesarean section for women with severe pre-eclampsia in a third world setting [63]	No	1156	Medical records
55	Retrospective evaluation of anesthesia approaches for lumbar disc surgery [64]	IEC	328	Medical records
56	Caesarean section for placenta praevia: A retrospective study of anesthetic management [65]	No	350	Medical records
57	Retrospective data collection and analytical techniques for patient safety studies [66]	No	277	Medical records
58	Anesthesia for awake craniotomy: A retrospective study of 54 cases [67]	IEC	54	Medical records
59	Anesthesia and cancer recurrence: What is the evidence? [68]	No	129	
60	A five-year retrospective study on the common microbial isolates and sensitivity pattern on blood culture of pediatric cancer patients admitted at the Philippine general hospital for febrile neutropenia [69]	No	90	Laboratory reports
61	Retrospective study on risk habits among oral cancer patients in Karnataka Cancer Therapy and Research Institute, Hubli, India [70]	No	1,472	Medical records
62	Oral cancer in the UAE: A multicenter, retrospective study [71]	No	992	Pathology reports
63	Incidence of second primary oral cancer tumors: A retrospective study [72]	IEC	34,637	Medical records
64	Survival of dental implants in patients with oral cancer treated by surgery and radiotherapy: A retrospective study [73]	Yes	34	Medical histories
65	Demographic and clinical profile of oral lichen planus: A retrospective study [74]	No	128	Pathology reports
66	Retrospective study of the frequency of oral squamous cell carcinoma in the population of Volta Redonda, Rio de Janeiro, Brazil [75]	No	5880	Pathology reports
67	Metabolic syndrome in adults with congenital heart disease [76]	IEC	150104	Treatment records

(*Contd...*)

Table 1: (*Continued*)

S.No.	Title of the study/reference	Informed consent	Number of subjects	Material used for study
68	High prevalence of cardiovascular diseases among other medically compromised conditions in dental patients: A retrospective study [77]	No	36,729	Medical records
69	Cardiovascular disease in asthma and COPD: A population-based retrospective cross-sectional study [78]	Yes	909,638	Medical records
70	A multicenter retrospective study defining the clinical and hematological manifestations of brucellosis and pancytopenia in a large series: Hematological malignancies, the unusual cause of pancytopenia in patients with brucellosis [79]	No	202	Medical records
71	Invasive infections caused by *Trichosporon* species and *geotrichum capitatum* in patients with hematological malignancies: A retrospective multi-centric study from Italy and review of the literature [80]	No	52	Laboratory reports
72	Respiratory diseases morbidity and mortality among adults attending a tertiary hospital in Nigeria [81]	IEC	183	Laboratory reports
73	Prevalence of respiratory diseases in hospitalized patients in Saudi Arabia: A 5 years study 1996-2000 [82]	No	810	Medical records
74	Drug utilization patterns in the emergency department: A retrospective study [83]	IEC	300	Medical records
75	Primary gastrointestinal non-Hodgkin's lymphoma: A retrospective study with emphasis on prognostic factors and treatment outcome [84]	No	208	Pathology reports
76	Gastrointestinal lymphomas: Pattern of distribution and histological subtypes: 10 years' experience in a tertiary center in South India [85]	No	361	Pathology reports
77	Pediatric anaphylaxis: A 5 year retrospective review [86]	IEC	117	Medical records
78	Interpretation of upper gastrointestinal tract endoscopic biopsies: A retrospective study [87]	No	100	Pathology reports
79	Retrospective study of cancer types in different ethnic groups and genders at Karachi [57]	No	5134	Medical histories
80	Primary extra nodal non-Hodgkin lymphoma: A 5 year retrospective analysis [88]	No	68	Pathology reports
81	Gastrointestinal stromal tumors and extra-gastrointestinal tract neoplasms [89]	No	21	Pathology reports
82	ACE gene polymorphism: Ischemic heart disease and longevity in 10 150 individuals: A case-referent and retrospective cohort study based on the Copenhagen city heart study [90]	IEC	7263	Medical records
83	New autoimmune diseases after cord blood transplantation: A retrospective study of EUROCORD and the Autoimmune Disease Working Party of the European Group for Blood and Marrow Transplantation [91]	Yes	726	Laboratory reports
84	Retrospective multivariate analysis of hepatic veno-occlusive disease after blood or marrow transplantation: Possible beneficial use of low molecular weight heparin [92]	No	462	Medical records
85	Bacteremia in hospitalized patients with malignant blood disorders: A retrospective study of causative agents and their resistance profiles during a 14-year period without antibacterial prophylaxis [93]	No	1402	Treatment records
86	Demographic and clinical profile of oral squamous cell carcinoma patients: A retrospective study [94]	IEC	295	Cancer registry
87	Oral squamous cell carcinoma: A retrospective study of 740 cases in a Brazilian population [55]	No	740	Medical records
88	Epidemiology of oral and pharyngeal cancer at the National Cancer Institute, Cairo [95]	Yes	71	Medical histories
89	A retrospective study of survival in breast cancer patients undergoing deuterium depletion in addition to conventional therapies [96]	No	232	Pathology reports
90	Malignant skin tumors in Misurata Cancer Center during 2011-2014 [97]	No	195	Pathology reports
91	Assessment of clinical diagnostic accuracy compared with pathological diagnosis of basal cell carcinoma [98]	IEC	367	Pathology reports
92	Pattern of skin cancer in South Western Saudi Arabia [99]	No	193	Pathology reports
93	Retrospective analysis of melanocytic lesions in children at the National Cancer Institute [100]	No	102	Medical records
94	A retrospective study of treatment of squamous cell carcinoma *in situ* [101]	IEC	239	Laboratory reports
95	A retrospective analysis of occupational exposure to pesticides as a possible risk factor for non-melanoma skin cancers [102]	No	124	Pathology reports
96	An epidemiological review of skin cancers in Malwa belt of Punjab India: A 3-year clinicopathological study [103]	IEC	52	Pathology reports
97	Dermatological malignancies in Kano, Northern Nigeria: A histopathological review [104]	No	125	Pathology reports
98	Epidemiology of nonmelanoma and melanoma skin cancer in Zagreb, Croatia [105]	No	16938	Pathology reports
99	Retrospective study of papulonodular skin lesions and their clinopathological correlation [106]	Yes	75	Laboratory reports
100	A retrospective study investigating the rate of HER2 discordance between primary breast carcinoma and locoregional or metastatic disease [107]	Yes	157	Pathology reports

evaluated in the retrospective studies. A record of informed consent from subjects or approval of study from the IEC was taken after the study was made.

RESULTS AND DISCUSSION

A total of 100 studies were reviewed. The informed consent was obtained in only 14% of studies and the rest 86% of the studies were conducted without the consent of the subjects and even the patient or subject might be unaware of their contribution in the research or their involvement in the studies. Of 100 only in 21 studies the approval from the ethical committee was taken. Only one study out of 100 studies has been conducted with patient information as well as ethical clearance from the Ethical Review Board. This clearly shows the poor status of informed consent in the studies with retrospective design (Fig. 1). It was also observed that on the whole around 65 studies out of 100 were conducted without the ethical approval and the consent of the patients. Moreover, these studies used the data of around approximately 2,509,099 patients. The total number of subjects who were informed regarding their involvement in the study is approximately 946,488. The rest of 1,562,611 patients were unaware about their participation in the study. The British Sociological Association's Statement of Ethical Practice [9] depicts that informed consent for use of data and any other material should be obtained by researchers without which the existence of basic ethical norms relating to clinical research and personal privacy will be contradicted. All other major regulatory authorities also emphasize the same point. However, in our results, it is very clearly reflected that the principles of protection of patient rights is deliberately violated.

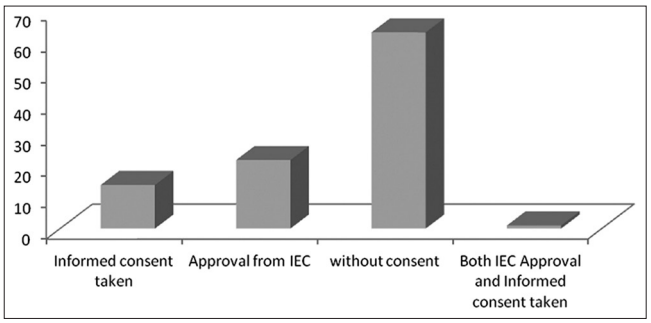

Figure 1: Status of informed consent in retrospective studies

Table 2: Data of material used and subject number for retrospective studies

Type of data	Number	Total number of subjects
Pathology reports	20	29,701
Medical records	42	1,742,136
Laboratory reports	13	6,824
Cancer registry	9	12,400
Treatment records	4	152,058
Prescription data	2	14,117
Internet/electronic search	5	12,400
Medical histories	5	505,306

In addition, other interesting information from study was that out of 100 studies around 50 studies are on cancer. This indicates that for cancer research, retrospective studies might play a great role. The data show that the commonly used material for the retrospective studies (Table 2) are pathology reports, medical record, laboratory reports, cancer registry data, treatment records, prescription data, and PubMed/Electronic search. In around 33 studies, the pathology and laboratory reports have been used, 42 studies involve the medical record of patients, 9 studies include cancer registry data, 6 involved the treatment records and prescription data and in only 5 studies the internet search/PubMed/electronic search was carried out. Results are suggestive of voracious use of medical records for retrospective studies.

Authors have also analyzed the number of publications published without the IEC approval against the Committee on Publication Ethics (COPE) regulations out of these 100 studies (Table 3). It clearly indicates 66% of papers in which informed consent and institutional ethical approval have not been taken for the retrospective study. If we go back in year 2000 then it is bit possible that papers could be published against COPE regulations but data of this study show that significant number of papers have been published without the informed consent and ethical approval even in 2011-2015. The COPE was found in 1997 to address breaches of research and publication ethics [108]. According to the COPE guidelines the good research should be well justified, well planned, appropriately designed, and ethically approved. Fully informed consent should always be sought. If according to the circumstances it is not possible to take informed consent the approval or decision from the ethics committee is acceptable. When participants are unable to give fully informed consent, research should follow international guidelines, such as those of the CIOMS. Authors for the publication of their work

Table 3: Year of publication of papers (out of n=100 studies) against COPE

Year of publication of study	Total no. of studies	IEC approval	Informed consent	No IEC/No informed consent	% studies published against COPE
2016	3	3	-	-	0
2015	17	5	5	7	41.1
2014	10	2	2	6	60
2013	9	1	1	7	77.7
2012	11	1	3	7	63.6
2011	9	1	1	7	77.7
2010	6	3	-	3	50
2009	6	3	1	2	33.3
2008	9	1	1	7	77.7
2007	2	-	-	2	100
2006	3	-	-	3	100
2005	2	-	-	2	100
2004	3	-	-	3	100
2003	2	-	-	2	100
2002	1	-	-	1	100
2001	3	-	-	3	100
2000	1	-	-	1	100
1998	1	-	-	1	100
1997	2	1	-	1	50
Total	100	21	14	65	65

COPE: Committee on Publication Ethics, IEC: Institutional Ethics Committee

must follow the World Medical Association's Declaration of Helsinki. The journals have a duty to consider the ethical aspects of both submitted and published work. It is required that every research article submitted to any journal must include a statement that the study obtained ethics approval including the name of the ethics committee or institutional review board and a statement that participants gave informed consent before taking part. The international committee of medical journal editors [109] states that the requirement for informed consent should be included in the journal's instructions for authors. Research should be conducted in accordance with the Helsinki and approval from IEC must be taken. However, our results are indicative that the publishing rules are also being violated. The publishing houses are publishing the paper even without the informed consent and institutional ethical approval.

Strength and limitations of the study

Strength of the study is that the objective parameter (informed consent/ethical clearance) is not affected by design of studies as the design in case-series study, cross sectional study, case control study and a historic cohort study are different. As this study represents limited data of 100 observational studies with retrospective design, the data may not be representative of all the retrospective studies conducted.

CONCLUSION

From the analysis it is clear that observational studies with retrospective design are of immense use for generating data; however, a conscious violation of rules and regulations have been made and is being made continuously by investigators for not taking informed consent/ethical approval of retrospective studies. Before the participation of subject in the research, the consent must be obtained so that the right of voluntariness is respected. Regulatory bodies must tighten the noose to ensure ethical clearance of all the retrospectively designed studies. It should be made mandatory for the journals to take the ethical clearance certificate from authors before publication of any study including human subjects.

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